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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Manfred BOHN et al.

Serial No. 09/077,194

Filing Date: May 26, 1998

For: USE OF 1-HYDROXY-2-PYRIDONES FOR THE TREATMENT OF SEBORRHEIC DERMATITIS

Group Art Unit: 1639

Examiner: Jon D. Epperson

Confirmation No. 5713

Mail Stop Appeal Brief - Patents
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

RE-SUBMISSION OF APPEAL BRIEF UNDER 37 C.F.R § 41.37

Pursuant to the March 6, 2009 Office communication, Applicant hereby respectfully re-submits the appeal brief with the corrected "statement of the status of the claims section" as follows.

Pursuant to the Notice of Appeal filed on July 24, 2007, Appellants submit this Appeal Brief in accordance with 37 C.F.R. § 41.37.

EXPRESS MAIL CERTIFICATE (37 CFR 1.10)

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I hereby certify that this paper, and the papers and/or fees referred to herein as transmitted, submitted or enclosed, are being deposited with the U.S. Postal Service "Express Mail Post Office to Addressee" service under 37 CFR § 1.10 on the date indicated above and is addressed to Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Name Cody M. Nye Signature Cody M. Nye

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I. Real Party in Interest

Sanofi-Aventis Deutschland GmbH is the assignee of record, as evidenced by the assignment recorded July 19, 2006, at Reel 017946, Frame 0877, and has licensed the invention under appeal to Medicis Pharmaceutical Corporation. As such, Sanofi-Aventis Deutschland GmbH and Medicis Pharmaceutical Corporation are both real parties in interest in this appeal.

II. Related Appeals and Interferences

With respect to appeals, interferences, or proceedings that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal, Appellants and Appellants' undersigned legal representative inform the Board of the Board's prior Decision in the present application, Appeal No. 2004-0309, mailed September 15, 2004, copy attached in the Related Proceedings Appendix at the end of this Brief. Appellants also filed an Appeal Brief on October 15, 2007, in related U.S. Application No. 10/606,229. The ongoing appeal in U.S. Application No. 10/606,229 has not yet been assigned an appeal number.

III. Status of Claims

Claims 38-42, 48, and 61-66 are pending and listed in the Claims Appendix of Part VIII. Claims 1-37, 43-47, 49-60 and 67 were canceled.

The Examiner has rejected claims 38-42, 48, and 61-66 under one or more of 35 U.S.C. §§ 112, first and second paragraphs, 102(b), and 103(a) and under the judicially created doctrine of obviousness-type double patenting.

Claims 38-42, 48, and 61-66 are the subject of this appeal. As argued below, Appellants believe that the rejected claims are patentable.

IV. Status of Amendments

All amendments have been entered. No amendments have been made subsequent to the Reply After Final Under 37 C.F.R. § 1.113 filed June 4, 2007.

V. Summary of Claimed Subject Matter

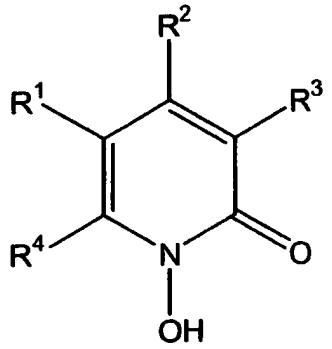
Seborrheic dermatitis ("SD") is a disorder of the scalp, which differs from dandruff by the presence of erythema (i.e., redness) as a sign of inflammation, by a greater degree of scaling with itching and burning, and by eczematous changes at other body sites besides the scalp. *See* specification at p. 1, ll. 3-7. On the scalp, SD can manifest in the form of patches, or affect the whole scalp and beyond, and can be accompanied by secondary infections. *Id.* at ll. 7-11. In contrast, dandruff is characterized by a clinically *noninflammatory* scaling of the scalp and occurs in almost all people. *Id.* at ll. 22-24 (emphasis added).

It is known that 1-hydroxy-2-pyridones exhibit activity against normal dandruff. *Id.* SD, however, was treated by other types of compounds, namely corticosteroids and antimycotics. *Id.* at ll. 26-28. The methods of the present invention use a single composition comprising as a sole active ingredient a 1-hydroxy-2-pyridone in the treatment of SD. The 1-hydroxy-2-pyridones described in the methods according to the invention as recited in the claims on appeal have several advantages over other treatments for SD. First, 1-hydroxy-2-pyridones exhibit both noninflammatory activity and antimycotic activity. *Id.* at ll. 30-37. Second, 1-hydroxy-2-pyridones have relatively broad anti-bacterial activity in that they are effective against Gram-positive and Gram-

negative aerobic and anaerobic bacteria, which can be important when, as often happens, secondary infections are involved in SD cases. *Id.* at p. 2, ll. 6-12. Finally, the solubility of 1-hydroxy-2-pyridones in water, alcohols, and aqueous-alcoholic solutions makes preparation of lotions and gels simpler. *Id.* at ll. 14-19.

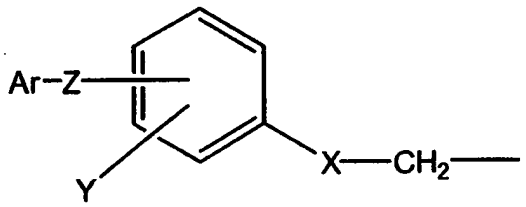
Independent claim 38 is directed to a method of treating seborrheic dermatitis in a human patient in need thereof comprising administering to the patient an amount effective for the treatment of seborrheic dermatitis of a single composition, wherein this composition comprises:

(A) a sole active component, which is a 1-hydroxy-2-pyridone of formula I or a pharmaceutically acceptable salt thereof:



(I)

where R^1, R^2, and R^3, which are identical or different, are H or alkyl having 1 to 4 carbon atoms, and R^4 is a saturated hydrocarbon radical having 6 to 9 carbon atoms or a radical of formula II:



(II)

where:

X is S or O;

Y is H, or 1 or 2 identical halogen atoms, or a mixture of 2 different halogen atoms;

Z is a single bond, or

a linking radical comprising

(1) O, or

(2) S, or

(3) $-CR_2-$, where R is H or (C_1-C_4)-alkyl, or

(4) from 2 to 10 carbon atoms linked in the form of a straight or branched chain, which optionally further comprises one or more of the following:

(i) a carbon-carbon double bond, and

(ii) O, S, or a mixture thereof, wherein if 2 or more O or S atoms or a mixture thereof are present, each O or S atom is separated by at least 2 carbon atoms; and,

in any of the foregoing linking radicals, any remaining free valences of the carbon atoms of said linking radical are saturated by H, (C_1-C_4)-alkyl, or a mixture thereof;

and

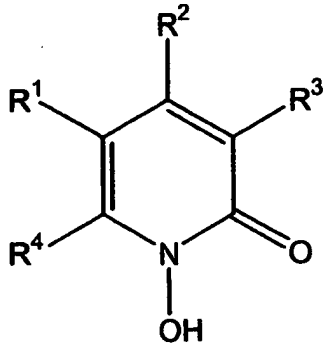
Ar is an aromatic ring system having one or two rings, the aromatic ring system being unsubstituted or substituted by one, two, or three radicals, which are identical or different, and are chosen from halogen, methoxy, (C_1-C_4)-alkyl, trifluoromethyl, and trifluoromethoxy; and

(B) at least one surfactant chosen from anionic surfactants, cationic surfactants, nonionic surfactants, and amphoteric surfactants; and

wherein the composition has a pH ranging from about 4.5 to about 6.5. *See, e.g.,* specification at p. 1, lines 34-37; p. 2, ll. 6-12; p. 2, l. 25 to p. 3, l. 18; p. 5, l. 37 to p. 6, l. 2; p. 8, ll. 29-33; and Examples 1-3.

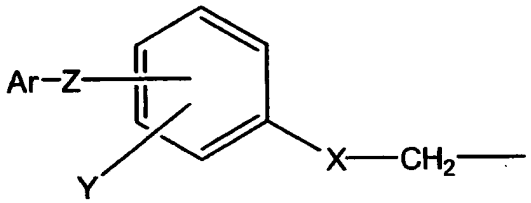
Independent claim 39 is directed to a method of treating seborrheic dermatitis in a human patient in need thereof comprising administering to the patient an amount effective for the treatment of seborrheic dermatitis of a single composition, wherein this composition comprises:

(A) a sole active component, which is a 1-hydroxy-2-pyridone of formula I or a pharmaceutically acceptable salt thereof:



(I)

where R^1, R^2, and R^3, which are identical or different, are H or alkyl having 1 to 4 carbon atoms, and R^4 is a saturated hydrocarbon radical having 6 to 9 carbon



(II)

atoms or a radical of formula II:

where:

X is S or O;

Y is H, or 1 or 2 identical halogen atoms, or a mixture of 2 different halogen atoms;

Z is a single bond, or

a linking radical comprising

(1) O, or

(2) S, or

(3) $-CR_2-$, where R is H or (C_1-C_4)-alkyl, or

(4) from 2 to 10 carbon atoms linked in the form of a straight or branched chain, which optionally further comprises one or more of the following:

(i) a carbon-carbon double bond, and

(ii) O, S, or a mixture thereof, wherein if 2 or more O or S atoms or a mixture thereof are present, each O or S atom is separated by at least 2 carbon atoms; and,

in any of the foregoing linking radicals, any remaining free valences of the carbon atoms of said linking radical are saturated by H, (C_1-C_4)-alkyl, or a mixture thereof;

and

Ar is an aromatic ring system having two rings, the aromatic ring system being unsubstituted or substituted by one, two, or three radicals, which are identical or different, and are chosen from halogen, methoxy, (C_1-C_4)-alkyl, trifluoromethyl, and trifluoromethoxy, and wherein Ar is a bicyclic system derived from biphenyl, diphenylalkane, or diphenyl ether; and

(B) at least one surfactant chosen from anionic surfactants, cationic surfactants, nonionic surfactants, and amphoteric surfactants.

See, e.g., id. p. 1, lines 34-37; p. 2, ll. 6-12; p. 2, l. 25 to p. 3, l. 18; p. 3, ll. 31-34; p. 5, l. 37 to p. 6, l. 2; and Examples 1-3.

VI. Grounds of Rejection to be Reviewed

Claims 38, 40-42, 48, and 65 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey that the inventors had possession of the claimed invention at the time the application was filed. Final Office Action dated January 25, 2007 ("Final Office Action"), at 3.

Claims 38-42, 48, and 61-66 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for the terms "pharmaceutically acceptable salt" and "seborrheic dermatitis." *Id.*, at 5-7.

Claims 39 and 61-64 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by WO 96/02226 ("*Lagarde*"). *Id.*, at 9.

Claims 39 and 62-64 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by WO 88/00041 ("*Lange*") as evidenced by Green People (www.greenpeople.co.uk/Oganics_Features_SLS.htm) ("*Green People*") and Avre Skin Care (www.avro.co.za/misc/about_skincare/cosmetic_ingredients.html) ("*Avre*"). Final *Id.*, at 13.

Claims 38-42, 48, 53-58, and 61-66 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over *Lange* and 56 FR 63568 ("*FDA*") and WO 96/29045 ("*Dascalu*") in view of *Green People*, *Avre*, Dreumex (www.signus.com/dsoftsoap.htm) ("*Dreumex*"), U.S. Patent 6,514,490 ("*Odds*") and Brinkster (www.misterguch.brinkster.net/acidtutorial.html) ("*Brinkster*"). *Id.*, at 17-18.

Claims 38-42, 48, and 61-66 stand rejected under 35 U.S.C. § 102(b) or alternatively under 35 U.S.C. § 103(a) as allegedly anticipated or obvious over EP

0117135 A2 ("*Verdicchio*") in view of Janniger et al. (American Family Physician, July 1995, pp. 149-55) ("*Janniger*") and U.S. Patent 4,185,106 ("*Dittmar*"). *Id.*, at 30.

Claims 38-42, 48, and 61-66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 14-23 and 26-29 of U.S. Application No. 10/606,229. *Id.*, at 27.

VII. Arguments

A. Rejection Under 35 U.S.C. § 112, First Paragraph: The Specification Supports a Sole Active Component as Recited in Independent Claim 38

The Examiner rejects claims 38, 40-42, 48, and 65 under 35 U.S.C. § 112, first paragraph, for allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) . . . had possession of the claimed invention." Final Office Action at 3; Advisory Action of July 16, 2007 ("Advisory Action"), at 2. According to the Examiner, claim 38 recites "a sole active component consisting of at least one 1-hydroxy-2-pyridone of formula I . . . in free form or as a pharmaceutically acceptable salt." *Id.*, emphasis in original. The Examiner, however, states that he cannot find support for a "pharmaceutically acceptable salt" because the specification allegedly states that "when using the compounds in salt form, the adjustment of the pH . . . has to be carried out using organic acids." *Id.* Citing page 7 of the *Lange* reference (see discussion of § 102(b) rejections below), the Examiner further contends that "organic acids, including lactic acid, are known to possess anti microbial action." Final Office Action at 3; Advisory Action at 3. Based on these alleged facts, the Examiner concludes that Applicant "[has] not shown where support for . . . compounds that contain[s] '1-hydroxy-

2-pyridone of formula I salt + non active organic acids' can be found." *Id.* Appellants disagree.

1. The Legal Standard for Written Description

To satisfy the written description requirement under 35 U.S.C. § 112, first paragraph, a patent *specification* must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicant was in possession of the invention as now claimed. See M.P.E.P. §2163.02. Here, Appellants submit that the Examiner improperly attempts to override the present specification's clear teaching with his own interpretation, citing to one isolated sentence out of *Lange* for "support." The focus of the written description requirement lies in what the specification at issue teaches, not what extrinsic evidence, such as a scientific article or another patent, purportedly says with respect to its own disclosure. As the M.P.E.P. instructs, the Examiner "must have a reasonable basis to challenge the adequacy of the written description. The Examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an Applicant's disclosure a description of the invention defined by the claims." M.P.E.P. § 2163.04. Taking a single sentence out of a reference, and applying it in a way that contradicts the rest of the teachings of that reference, does not constitute a "reasonable basis" for challenging the adequacy of the specification's written description.

2. The Presence of an Organic Acid as a pH Adjuster Does Not Act as an Anti-seborrheic Agent

At the heart of this rejection is the Examiner's attempt to make the case that, in addition to the 1-hydroxy-2-pyridone recited in claim 38, any organic acid(s) used for pH

adjustment would also act as an active ingredient. Because claim 38 recites a "pharmaceutically acceptable salt," the Examiner assumes that organic acids must be present in the described composition based on the following passage at page 8, lines 30-33 of the present specification: "[w]hen using the compounds in salt form, the adjustment of the pH range mentioned has to be carried out using organic acids. . . . " The Examiner couples this passage with a single statement in *Lange* about using organic acids in phase II (described below) of their product, noting that "organic acids in the phase II composition, which acids *per se* possess an anti microbial action." *Lange*, at 7, last paragraph.

As stated above, the specification is the key to determining whether the written description requirement under 35 U.S.C. § 112, first paragraph, has been met. At page 8, lines 30-33, the present specification explains that "[w]hen using the compounds in salt form, the adjustment of the pH range mentioned has to be carried out using organic acids. . . . " This instruction says nothing about using organic acids as an active ingredient in the treatment of SD. Rather, this instruction simply informs the skilled artisan that, when a salt form of the 1-hydroxy-2-pyridone described in claim 38 is used in the invention, one should use an organic acid to adjust the pH. The skilled artisan would know that given the level of acid dilution that would occur when one uses an acid to adjust pH, any alleged antimicrobial activity it might have would not survive such a dilution. On this basis alone, one of ordinary skill in the art would recognize that Appellants were in possession of a composition in which the sole active component is a 1-hydroxy-2-pyridone as described in claim 38. And if one considers the *entirety* of

Lange, and not only the one sentence relied on by the Examiner, this reference supports the specification's teaching on this point, as Appellants will now explain.

Lange as a whole describes the use of a two-composition system to treat dandruff. The first composition, "phase I," is a detergent composition with a pH preferably in the neutral or weakly alkaline range. *Lange* at 6. The second composition, "phase II," "contains a solution of physiologically acceptable organic acid or mixture of these acids" and does not contain detergents. *Id.* at 3, second paragraph, and at 9, third paragraph. In discussing these two compositions, a detergent-containing shampoo and an acid-containing rinse, *Lange* clearly instructs that "soaps are not well suited for making lower pH products. . . Thus, the simultaneous action of the two previously mentioned compositions included in one shampoo is practically not feasible." *Id.* at 4, second full paragraph, emphasis added.

Therefore, *Lange*'s invention requires the use of two separate compositions, packed separately ". . . because both compositions may not be mixed without loss of effectivity . . . and because the synergistic effect of the components used in both liquids is only obtained if they are used one directly after the other!" *Id.* at 11, last paragraph, emphasis original. In other words, *Lange* teaches that when the acid is mixed with a detergent-containing solution, any alleged antimycotic effect is destroyed. Based on *Lange*'s teaching that the surfactant composition I must be kept separate from the acid composition II, one of ordinary skill in the art cannot conclude that an organic acid, when added to such a surfactant composition, would retain its alleged antimycotic activity, i.e., would still behave as an active ingredient. Thus, the entirety of *Lange* does not show that organic acids, *per se*, have antimicrobial activity. The Examiner contends

that *Lange* used organic acids to adjust the pH of the phase II composition. Advisory Action at 4. Even if this were true, it does not change the fact that the phase I composition and the phase II composition cannot be mixed without loss of antimycotic activity, according to *Lange*.

Appellants also wish to clarify the Examiner's misinterpretation of claim 38. Specifically, the Examiner states that claim 38 does not state that the described composition comprises a sole active ingredient against SD. Advisory Action at 4. Based upon this interpretation, the Examiner concludes that the claims preclude the use of all other active components whether they are useful in treating SD or not. *Id.* Appellants disagree with this interpretation of the claims. The Examiner's interpretation of claim 38 improperly considers this claim in a vacuum, rather than in light of specification's teachings on the treatment of SD. Moreover, claim 38 itself indicates that the "active component" is active against SD. Specifically, claim 38 recites "[a] method of treating seborrheic dermatitis in a human patient in need thereof comprising administering to the patient an amount effective for the treatment of seborrheic dermatitis of a single composition, wherein this composition comprises: . . . a sole active component . . . . " The preamble of claim 38 clearly connects the treatment of SD with the composition administered to the patient. The sole "active" ingredient in this composition to treat SD is an ingredient that is active against SD.

In sum, when reading the specification and the entirety of *Lange*, one of ordinary skill in the art would recognize that Appellants were in possession of a method of treating SD that uses a single composition comprising a sole active component, which is a 1-hydroxy-2-pyridone as described in independent claim 38. Because claims 38 and

its dependent claims 40-42, 48, and 65 are supported by the specification, the Board should reverse this rejection.

B. Rejections Under 35 U.S.C. § 112, Second Paragraph: Claims 38-42, 48, and 61-66 Are Definite

1. The Term "Pharmaceutically Acceptable Salt" Is Clear

Claims 38-42, 48, and 61-66 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite for reciting the phrase "pharmaceutically acceptable salt." According to the Examiner, the "pharmaceutically acceptable salt" embodiment "requires two active ingredients, (1) the salt of a compound of formula I and (2) the organic acid that is used to adjust the pH." Final Office Action at 6; Advisory Action at 5-6. In light of this interpretation, it is not clear to the Examiner "how the composition comprises a 'sole' active ingredient[s] when more than one active ingredient[s are] is being claimed." *Id.*

This indefiniteness rejection is effectively an extension of the Examiner's written description rejection above. Because claim 38 and 39 recite a "pharmaceutically acceptable salt," the Examiner concludes that the composition must have organic acid in it. Appellants contend that if the composition has organic acids in it, the acid is there merely to adjust the pH, as taught by the specification. Using his incorrect interpretation of *Lange*, the Examiner appears to reason that if an organic acid must be present due to the use of a salt form, then there must be more than one active ingredient according to *Lange*. Thus, in the Examiner's view, it is confusing how claim 38 and 39 can recite a sole active ingredient and a pharmaceutically acceptable salt at the same time.

Independent claim 38 does not require two active ingredients as the Examiner suggests. As Appellants explained above in Section (VII)(A)(2), *Lange* shows that an organic acid loses its antimycotic activity when mixed with a detergent. Thus, the organic acid, even if it were present in the composition of claims 38 and 39, would not be an active ingredient against SD. This is consistent with claim 38 and 39, which describe describes a composition in which a 1-hydroxy-2-pyridone is the sole active ingredient. Neither the specification nor *Lange* teach that an organic acid, when used adjust the pH of a detergent-containing composition, has an antimicrobial effect. Thus, the phrase "pharmaceutically acceptable salt" is not indefinite and the Examiner's rejection should be reversed.

2. The Term "Seborrheic Dermatitis" Is Clear and Has Been Used Consistently Throughout the Prosecution History

The Examiner also rejects claims 38-42, 48, 53, 55-59, and 61-67 as allegedly indefinite because the term "seborrheic dermatitis" is allegedly unclear in light of the prosecution history. According to the Examiner, *Dascalu* teaches the treatment of the "same exact symptoms as defined in Applicant's specification" and "that their treatment inhibits the exact yeast, Pityrosporum." Final Office Action at 7; Advisory Action at 7. Thus, the Examiner concludes, "it is not clear what symptoms, underlying causative agents and/or other physiochemical factors Applicants are relying on to make this distinction." *Id.*

When interpreting the meaning of a term in a claim, the Examiner should turn to the specification. Like the written description rejection discussed above, this indefiniteness rejection is another example of the Examiner's attempt to imprint his own

thinking over the teaching of the specification. Indeed, Appellants note that during the first appeal of this application, the Board turned immediately to the specification for guidance on the meaning of the term "seborrheic dermatitis." See Board's decision in Appeal No. 2004-0309, dated September 15, 2004, at 5. Thus, the Board has in the past acknowledged that the specification teaches a difference between SD and dandruff. *Id.* To assist the Examiner's understanding of this term, Appellants submitted a series of declarations that further describe the condition of SD.

As discussed above and on the record, the specification explains that SD is a condition of the scalp that differs from simple dandruff in that it is characterized by "erythema[, a] greater degree of scaling with occasional itching and burning, and by the occurrence of eczematous changes in other body sites." Specification, at 1, lines 3-11. Over the course of prosecution of this application, Appellants have submitted a series of declarations designed to further describe SD. The declaration of Dr. R. Todd Plott, dated July 17, 2006, was submitted in an Information Disclosure Statement in the present case on September 22, 2006. Dr. Plott, who is a board certified dermatologist and one of ordinary skill in the art, explains in his declaration that "dermatologists know that seborrheic dermatitis is an inflammatory disorder associated with the hyperproliferation of keratinocytes, while dandruff is a 'noninflammatory' scaling of the scalp. While both disorders can include flaking skin among their symptoms, they are known by dermatologists to be different disorders." Plott Declaration at 2. The Examiner noted in the Advisory Action that "it is interesting that Applicants' specification never mentions this important 'hallmark' (i.e., if 'hyperproliferation of keratinocytes' is the 'hall mark' that distinguishes seborrheic dermatitis from dandruff then why doesn't

the specification even mention it.") Advisory Action at 8-9. Appellants respectfully remind the Examiner that the inventor may describe the invention in any way he sees fit. Moreover, the specification was written with the knowledge of one of ordinary skill in the art in mind, i.e., the knowledge that a dermatologist would know. The declarations that Appellants submitted were for the Examiner's benefit, to educate him on that knowledge. Appellants discuss these declarations and show that their combination with the specification renders a consistent image of what SD is.

Likewise, Dr. James Leyden, who is a practicing dermatologist and one of ordinary skill in the art, instructs in his declaration dated January 4, 2006, submitted in an Information Disclosure Statement on September 22, 2006, that SD is a "disorder characterized by the hyperproliferation of keratinocytes in the skin. It is characterized by erythema (redness of the skin), scaling and yellow crusted patches. . . . Essentially, in seborrheic dermatitis, the epidermal keratinocytes multiply too quickly, causing scaling and other symptoms." Leyden declaration at 2.

Appellants also submitted a declaration by Dr. Mitchell S. Wortzman on June 9, 2003, during the first appeal of the present case. Appellants note that, during this first appeal, the Board entered this declaration into the record. Dr. Wortzman has a Ph.D. in cellular and molecular biology and has been involved in research and development for numerous dermatological products. Dr. Wortzman's declaration, dated June 6, 2003, explains that "dandruff is a 'noninflammatory' scaling of the scalp, while 'seborrheic dermatitis is an inflammatory erythematous, and scaling eruption that occurs in seborrheic areas . . . such as the scalp, face, and trunk.'" Wortzman declaration at 2. The Wortzman declaration further teaches that "even the scales of dandruff look

different from the scale from seborrheic dermatitis; dandruff has thin, white or gray flakes, while seborrheic dermatitis has oily, yellowish scales with inflammation." *Id.*

Each of the above descriptions contributes to a single, consistent description and definition of SD. In contrast, *Dascalu* does not describe the hyperproliferation of keratinocytes or the presence of "crusted patches" on the skin. Also, while *Dascalu* appears to generally describe scaling of the skin, *Dascalu* does not mention the "hyperproliferation of keratinocytes" that is the hallmark of SD (as noted by Dr. Leyden), nor does *Dascalu* teach "oily, yellowish scales," which result from this condition. The term "seborrheic dermatitis" is not indefinite, but rather is clearly defined in the specification and by the intrinsic evidence of record. Appellants accordingly request that the Board reverse this rejection.

C. Rejections Under 35 U.S.C. § 102(b)

1. Claims 39 and 61-64 Are Novel in Light of *Lagarde*

a) The Legal Standard for Anticipation

A claim is anticipated under 35 U.S.C. § 102(b) only if each and every element as set forth in the claim is found in a single reference. *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987) and M.P.E.P. § 2131. Furthermore, the identical invention must be set forth in as complete detail as it appears in the claim. See *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989) and M.P.E.P. § 2131. *Lagarde* cannot be said to anticipate the present invention because it does not disclose each and every element of the present claim, even when one takes the Examiner's supporting references into account.

b) The Examiner's Rejection

The Examiner rejects claims 39 and 61-64 under 35 U.S.C. § 102(b) as anticipated by *Lagarde* in view of two online sources, Wikipedia and *Green People*. The Examiner contends that *Lagarde* teaches a method for treating seborrheic dermatitits in a human patient in need thereof using a "combination product comprising an anti-fungal agent selected from the 1-hydroxy-2-pyridones such as ciclpirox [sic] or octopirox and, secondly, crotamiton as an antifungal agent activity enhancer." Final Office Action at 10; Advisory Action at 11. *Lagarde* also allegedly teaches, according to the Examiner, "at least one 1-hydroxyl-2-pyridone of formula I as the sole active component . . . . " and "the use of a surfactant . . . (. . . Cocamide DEA, Cocamide MEA, Cocamidopropyl betaine are disclosed)." Final Office Action at 10-11; Advisory Action at 11-12. Acknowledging that *Lagarde* does not state that Cocamide DEA, Cocamide MEA and Cocamidopropyl betaine are surfactants, the Examiner relies on an entry from Wikipedia to suggest that "these would be inherent properties of these molecules." Final Office Action at 11; Advisory Action at 12. The Examiner also points to *Green People* to allegedly show that sodium lauryl sulfate is an "anion surfactant" that is included in a variety of commonly used products including shampoo. *Id.* Regarding claim 61, *Lagarde* allegedly discloses the "cyclohexyl R4 group." *Id.* Regarding claim 64, *Lagarde* allegedly discloses "at least one 'additional' surfactant such as cocamidopropyl betaine + Cocamide MEA." *Id.* Appellants respectfully disagree with the rejection.

c) *Lagarde* Does Not Teach a Single Composition with a Sole Active Ingredient

The composition described in independent claim 39 contains "a sole" active ingredient, 1-hydroxy-2-pyridone. As the Examiner has acknowledged, *Lagarde* teaches a combination product that contains two active ingredients, 1-hydroxy-2-pyridone and crotamiton as an antifungal agent. And, as Appellants have argued on the record, *Lagarde* requires that his composition be a combination product that benefits from the "synergic association of products [the 1-hydroxy-2-pyridone and crotamiton]." *Lagarde* translation at 6. Indeed, *Lagarde* does not teach or even remotely suggest non-combination products, i.e., a "single" composition comprising a "sole" active component, or the use of 1-hydroxy-2-pyridones as a sole active component. Instead, *Lagarde* is entirely focused on the synergism resulting from the combination of his two active ingredients, i.e., the treatment of "skin fungal infections" with a composition comprising two separate compounds - 1-hydroxy-2-pyridone and crotamiton. *Id.* In contrast, the method of present claim 39 describes administering to the patient a single composition with a sole active component. The secondary references cited do not remedy the shortcomings of *Lagarde* in this regard.

Because *Lagarde* describes a "combination product" with more than one active ingredient and does not teach each and every element of independent claim 39 as required for a proper anticipation rejection, this reference does not and cannot anticipate claim 39 and its dependent claims 61-64. This rejection is simply not supported by *Lagarde* and therefore should be reversed by the Board.

2. Claims 39 and 62-64 Are Novel in Light of *Lange*

a) The Examiner's Rejection

The Examiner rejects claims 39 and 62-64 under 35 U.S.C. § 102(b) as allegedly anticipated by *Lange* "as evidenced by" *Green People* and *Avre*. Final Office Action at 13; Advisory Action at 13-14. The Examiner describes *Lange* as disclosing "a two phase cleansing, conditioning and medicinal treatment shampoo and methods of use. . . for treating seborrheic dermatitis." Final Office Action at 13; Advisory Action at 14, emphasis in original. *Lange* also allegedly teaches that the phase I composition "may contain anti-mycotics in the medicinal as well as the anti-dandruff variant" and that "one may use a water soluble anti-mycotic such as piroctone olamine." Final Office Action at 14; Advisory Action at 14. *Lange* also allegedly teaches sodium lauryl sulfate, which the Examiner contends is inherently an anionic surfactant "as exemplified by Green People" and "at least one 'additional' surfactant such as lauramide DEA," which the Examiner also contends is inherently a surfactant "as exemplified by Avre Skin Care." Appellants respectfully disagree with the rejection.

b) *Lange* Does Not Teach a Single Composition with a Sole Active Ingredient

Lange first appeared in the prosecution history of the present application in an Office Action mailed on October 24, 2001 at page 3. This reference has been cited as U.S. Patent 5,132,107 and currently, as WO 88/00041. Both U.S. Patent 5,132,107 and WO 88/00041 are in the same patent family and thus the arguments that Appellants made against U.S. Patent 5,132,107 in the prosecution history also apply to the WO 88/00041 publication. Despite the fact that the Board vacated a rejection that used

Lange as the central reference and noted, in its previous opinion in this case, that *Lange* was not the closest prior art, the Examiner continues to use *Lange* as a basis for anticipation. See Appeal Brief filed on December 16, 2002, at 6 and BPAI Decision mailed September 15, 2004 in Appeal No. 2004-0309, at 2 and 14.

As Appellants have consistently argued on the record and as discussed above in Section VII.A.2 of this brief, *Lange* teaches a product made of two separate compositions or phases. *Lange*'s first composition, phase I, has a neutral or weakly alkaline pH of 7.5-8.5 and contains detergents. *Lange*'s second composition, phase II, has an acidic pH and is applied separately, after the first composition was applied and rinsed out. Most importantly, *Lange* clearly teaches that combining phase I and phase II into a single composition is "not feasible." *Lange* at 4. Instead, *Lange* teaches that the two phases should not be packed together because "both compositions may not be mixed without loss of effectivity." *Lange* at 11. Clearly, *Lange* does not teach a single composition as recited in rejected claim 39. On this basis alone, *Lange* does not anticipate claims 39 and 62-64.

The Examiner, however, takes issue with Appellants' position on *Lange*. In the Advisory Action, the Examiner argues that present specification requires "multiple application[s] of the composition" to be applied over a period of time (e.g., a week), and concludes that "the claimed method of treating seborrheic dermatitis comprising the use of a single composition must not be construed to preclude the application of more than one composition later in time. Furthermore, Applicants[‘] use of 'comprising' open-ended terminology . . . would not preclude the use of 'additional' ingredients to those 'later' compositions." Advisory Action at 16-17. However, the issue is not whether the

same single composition is applied multiple times over a period of time for treatment, but instead whether, ***each time*** the treatment is administered, multiple compositions have to be applied at a single sitting. *See, Lange*, abstract, discussing the application of shampoo in two steps (referred to as phases), one following the other, to allow "sequential application of noncompatible substances." The present claims require application of one composition for treatment, not two or more. Accordingly, the rejection over *Lange* should be withdrawn for this reason alone.

Finally, even if one were to try and make a single composition from the two separate phases taught in *Lange*, the skilled artisan would have to pick and choose specific elements from *Lange* to arrive at the claimed single composition. *See* Amendment filed on April 24, 2002, at 21. Such picking and choosing, without guidance in the reference as to which elements should be combined, is not a proper foundation for anticipation. *Id.*, citing M.P.E.P. § 2131. If anything, *Lange* expressly counsels against making the combination described in the rejected claims. If the Examiner were to interpret *Lange* as teaching a single composition, that interpretation would impermissibly change the principle of operation of a 2-step treatment.

For all of these reasons, *Lange* does not anticipate claims 39 and 62-64. Appellants therefore request that this improper rejection be reversed.

D. Rejection Under 35 U.S.C.§ 103(a): Claims 38-42, 48, 53-58, and 61-66 Are Patentable Under 35 U.S.C. § 103(a) Over *Lange*, *FDA*, and *Dascalu* in view of *Green People*, *Avre*, *Dreumex*, *Odds*, and *Brinkster*

Claims 38-42, 48, 53-58, and 61-66 stand rejected under 35 U.S.C. § 103(a) as obvious over *Lange*, *FDA*, and *Dascalu* in view of *Green People*, *Avre*, *Dreumex*, *Odds*,

and *Brinkster*. Appellants respectfully submit that the Examiner has not established a *prima facie* case of obviousness; therefore, this rejection is legally improper and should be reversed.

1. The Legal Standard for Obviousness

Several basic factual inquiries must be made in order to determine the obviousness or non-obviousness of claims of a patent application under 35 U.S.C. § 103. These factual inquiries, set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), require the Examiner to:

(1) determine the scope and content of the prior art;

(2) ascertain the differences between the prior art and the claims in issue;

(3) resolve the level of ordinary skill in the pertinent art; and

(4) evaluate evidence of secondary considerations.

The obviousness or non-obviousness of the claimed invention is then evaluated in view of the results of these inquiries. *Graham*, 383 U.S. at 17-18, 148 USPQ 467; *see also KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1734 (2007). As the M.P.E.P. provides, "when considering the obviousness of a combination of known elements, the operative question is thus 'whether the improvement is more than the predictable use of prior art elements according to their established functions.'" M.P.E.P. § 2141. In other words, "in short, the focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge." *Id.*

2. The Examiner Has Not Established A *Prima Facie* Case of Obviousness

a) The Examiner's Position

Lange, *Green People*, and *Avre* have already been discussed above with respect to the rejections under 35 U.S.C. §112 (*Lange)* and §102 (all three). Regarding claim 38, the Examiner alleges that *Lange* "does not teach the use of a pH range between about 4.5 to about 6.5" and "only teaches a 'neutral' pH." Final Office Action at 20; *see also* Advisory Action at 20. Citing to *Dreumeux* and *Odds*, the Examiner contends that "a pH range between 6-8 is generally considered to be neutral for shampoo products." *Id.* Thus, the Examiner concludes, "Lange teaches a pH range that overlaps in scope with the present invention (i.e., pH 6-8 overlaps in scope with a pH of about 4.5 to about 6.5." *Id.* According to the Examiner, where the claimed ranges overlap or lie inside ranges disclosed in the prior art or are close enough that one skilled in the art would expect them to have the same properties, a case of obviousness exists. *Id.* at 21; *see also* Advisory Action at 21. The skilled artisan would allegedly "expect pirocton olamine to have the same anti-mycotic properties whether it was at a neutral pH (6-8) or more acid pH (4-5)." *Id.* The skilled artisan would allegedly have been motivated to adjust the pH to 4-5 using lactic acid because of its "favorable bacterio and mycostatic properties." *Id.* at 22; *see also* Advisory Action at 22.

The Examiner also notes that while *Lange* and the *FDA* reference "fail to teach the use of a cyclohexyl radical," *Dascalu* allegedly teaches this. *Id.* at 20-22; *see also* Advisory Action at 21-22. The Examiner concludes that it would have been obvious to use ciclopiroxolamine in the treatment described in *Lange* and *FDA* because *Dascalu*

"explicitly states that ciclopiroxolamine is useful for this purpose." *Id.* at 23; *see also* Advisory Action at 23. In the Examiner's view, a motivation to make this combination lies in *Dascalu*'s alleged teaching that these compounds are a "preferred embodiment." *Id.*; *see also* Advisory Action at 23. The Examiner also suggests that the skilled artisan would have reasonably expected to be successful because *Dascalu* allegedly teaches "several successful examples of using anti-fungal agents like ciclopiroxolamines . . . and it is structurally related to the anti-fungal agents disclosed by the combined references of Lange and FDA." *Id.*; *see also* Advisory Action at 23.

In addition, the Examiner concedes that *Lange* "fails to recite the use of a keratolytic agent." *Id.* at 22; *see also* Advisory Action at 21. The Examiner believes, however, that it would have been obvious to use keratolytic agents "because the FDA explicitly approved this ingredient for its use in treating dandruff and seborrheic dermatitis." *Id.*; *see also* Advisory Action at 22. The skilled artisan would allegedly have been motivated to use salicylic acid with the treatment of *Lange* because "the FDA states that active ingredients like salicylic [sic] acid are 'recognized as safe and effective'" and have had a reasonable expectation of success "because the FDA approved the use [of] keratolytic agents like salicylic [sic] acid for the treatment of dandruff and seborrheic dermatitis and also shows its use with pyrithion zinc, which is . . . disclosed as a preferred embodiment of Lange." *Id.*; *see also* Advisory Action at 22. Appellants traverse this rejection.

b) *The improvement provided by the invention is more than the "predictable use of prior art elements."*

When determining whether an invention is obvious, the Examiner must ask whether the improvement provided by the invention is more than the predictable use of prior art elements according to their established functions. M.P.E.P. §2141, citing *KSR v. Teleflex*,82 USPQ2d at 1396, 127 S.Ct. at 1731 (2007). As Appellants argued in detail above, *Lange* clearly teaches that one phase containing a detergent and a second phase containing an organic acid cannot be mixed together without loss of effectivity. In *Lange*'s words, such a combination is not feasible. In contrast, the claimed invention recites a method of treating SD using the combination of a single composition that has an acidic pH and at least one surfactant chosen from anionic surfactants, cationic surfactants, nonionic surfactants, and amphoteric surfactants. Such a combination, according to *Lange*, should not work. Indeed, the skilled artisan would not have "reasonably expected to have been able to" use anionic surfactants, cationic surfactants, nonionic surfactants, and amphoteric surfactants in an acidic composition in view of what the skilled artisan knew at the time of the invention, e.g., based on reading *Lange*. See M.P.E.P. § 2141. Appellants note that the Examiner has not offered any support to show that the skilled artisan would have "reasonably expected to have been able to" use anionic surfactants, cationic surfactants, nonionic surfactants, and amphoteric surfactants in an acidic composition. Thus, *Lange*, the principal reference of this rejection, expressly teaches away from the claimed invention, i.e., the combination of a particular composition at acidic pH and a surfactant as claimed. As Appellants noted above, one of ordinary skill in the art would have learned

from *Lange* that a composition containing detergents or surfactants cannot be mixed with an acidic composition to yield a product that is effective for treating SD. Clearly, then, the improvement provided by the presently claimed invention is more than the predictable use of prior art elements according to their established functions.

Adding *FDA*, *Dascalu*, *Green People*, *Avre*, *Dreumex*, *Odds*, and *Brinkster* does not compensate for *Lange*'s teaching away from the invention. One of ordinary skill in the art would not have applied *Dascalu* to the claimed invention, because *Dascalu* teaches compositions containing two active ingredients, a cytotoxic agent and an antifungal agent for treating dandruff, which is a different condition from SD. See Amendment filed on April 24, 2002, at 19 and Reply filed June 4, 2007, at 19. Thus, *Dascalu* does not address compositions in which a 1-hydroxy-2-pyridone is the sole active ingredient against SD nor does this reference teach the combination of an acidic pH, the active ingredient and surfactants all in a single composition even for treatment of dandruff, let alone for the treatment of SD.

As Appellants have noted on the record, the other references cited by the Examiner, *Green People* and *Avre* provide generic background information on certain chemical agents such as sodium laurel sulfate and lauramide DEA. Reply filed June 4, 2007, at 20. These references have no link to a method of treating SD or to the single composition described in claims 38 and 39. *Brinkster* and *Dreumex* appear to provide general background information on the pH scale and the pH of *Dreumex* soap in particular. *Id.* Again, neither of these references has anything to do with a method for treating SD or with the single composition described in claims 38 and 39. *Odds*, like

Lagarde and *Lange*, teaches a combination product, emphasizing the importance of using both components together rather than alone. *Id.*

In contrast to the art cited by the Examiner, the rejected claims recite a method of treating SD using a single composition comprising as a sole active component a 1-hydroxy-2-pyridone.

As the Supreme Court instructed in *KSR*, the factual inquiries provided in *Graham v. John Deere Co.*, continue to apply to the analysis of obviousness. Among these factual inquiries is evidence of secondary considerations, including evidence of commercial success. *See also* M.P.E.P. § 2141. Appellants presented such evidence in a declaration by Mr. Kevin Kriel, attesting to the commercial success of compositions comprising 1-hydroxy-2-pyridone with the claim limitations, using Loprox® Shampoo as an example. The Examiner contends that Appellants have not addressed his "commensurate in scope" and "advertising" arguments in the Final Office Action. *See* Advisory Action at 25 and Final Office Action at 26-27. In the Final Office Action, the Examiner opined that Mr. Kriel stated that "ciclopirox, not all of the currently claimed 1-hydroxy-2-pyridones of formula I, has allegedly produced the increased sales." Final Office Action at 27. Thus, the Examiner concludes, Mr. Kriel's declaration "at best only provides support for ciclopirox." *Id.* The Examiner also suggested that there was "no evidence showing that success was attributable to the merits of Appellant's invention rather than to other factors such as advertising." *Id.* Appellants disagree.

Appellants have explained on the record that advertising alone would not speak to the repeat sales described in Mr. Kriel's declaration. See Supplemental Response filed September 22, 2006, at 8. Advertising may encourage new customers to buy a

product, but if the product is not of good quality and effect, they will not buy more of the product. Loprox® Shampoo is merely an example of these compositions. Thus, Mr. Kriel's declaration provides information on commercial success that is commensurate in scope with the claims on appeal.

In sum, because the Examiner's central reference, *Lange*, expressly teaches away from the claimed invention and the secondary references cited by the Examiner do not remedy this, the invention provides more than "the predictable use of prior art elements" and is not obvious in light of the references cited by the Examiner. Thus, the Examiner has not set forth a *prima facie* case of obviousness. Even if a *prima facie* case of obviousness had been established, Appellants have offered sufficient evidence of commercial success to overcome an obviousness rejection. Because this rejection is not supported by the cited references, the Board should remove this rejection.

E. Claims 38-42, 48, and 61-66 Are Patentable Under 35 U.S.C. § 102(b) or Alternatively Under 35 U.S.C. § 103(a) Over *Verdicchio* in view of *Janniger* and *Dittmar*

According to the Examiner, *Verducchio* discloses "a composition for treating dandruff in a human patient," but "do[es] not explicitly state that these people have seborrheic dermatitis." Final Office Action at 30; *see also* Advisory Action at 26. Relying on *Janniger*, the Examiner suggests that treatment of seborrheic dermatitis "is inherently disclosed because dandruff is a form of Seborrheic Dermatitis." *Id.*; *see also* Advisory Action at 26. *Verdicchio*'s composition allegedly "comprises a sole active component which is hydroxy pyridone such as Octopirox," which "falls within the scope of Applicants' formula I." *Id.* at 30 and 31; *see also* Advisory Action at 26 and 27. The Examiner also suggests that *Verdicchio* discloses "a pH of 'about' and wherein the

composition has pH ranging from about to about 4.5 to 6.5." *Id.* at 31; *see also* Advisory Action at 27. Appellants disagree.

1. *Verdicchio* Does Not Anticipate Claims 38-42, 48, and 61-66

Verdicchio does not teach a method of treating SD. Rather, *Verdicchio* consistently discusses treating dandruff, which is a separate condition from SD, as discussed by Applicant in Section V above and in the declarations discussed in this Appeal Brief. Thus, *Verdicchio* does not inherently teach a method of treating SD and as a result does not teach each and every element of claims 38-42, 48, and 61-66. The Examiner's reliance on *Janniger* is misplaced, because *Janniger* improperly confuses the term "dandruff" with the term "seborrheic dermatitis." The Examiner contends that there is no evidence that *Janniger* confused the definition of SD, but that *Janniger* "merely decided to use a broader definition." Advisory Action at 30. As Appellants explained above with regard to written description, the specification is the most important source for understanding and construing the claimed invention. When considering the term "seborrheic dermatitis," the Board, in the prior appeal in the present case, also turned to the specification rather to extrinsic evidence such as other scientific articles. The use of *Janniger* is yet another example of how the Examiner chooses to override the specification's teaching. SD and dandruff are two different conditions, as the specification teaches, and a reference such as *Verdicchio* that teaches treatment of one (dandruff) does not necessarily teach treatment of the other (SD), unlike the Examiner assumes. In the present case, *Verdicchio* does *not* teach treatment of both conditions and nowhere does it teach SD treatment. Thus, *Verdicchio* does not anticipate claims 38-42, 48, and 61-66.

Moreover, even if one were to consider dandruff as a symptom of SD, which Appellants do not, a reference that may speak to treating a symptom of SD does teach treating SD itself. As Appellants have explained on the record, independent claims 38 and 39 speak to the treatment of a human patient for the disease of SD, and not just a symptom of the disease. *See* Preliminary Amendment filed on February 22, 2005, at 22-24. The preamble of claims 38 and 39 recites: "A method of treating seborrheic dermatitis in a human patient in need thereof." Significantly, the Federal Circuit has held that similar language distinguishes the treatment of a disease from the treatment of mere symptoms of that disease.

In *Jansen v. Rexall Sundown, Inc.*, the Federal Circuit's claim construction as a matter of law illuminates the claim language of claims 38 and 39. See *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 68 U.S.P.Q.2d (BNA) 1154 (Fed. Cir. 2003). *Jansen's* preamble recited: "*A method of treating* or preventing macrocyclic megaloblastic anemia *in humans* . . . which comprises *administering* a daily oral dosage of a vitamin preparation *to a human in need thereof* . . . ." *Jansen,* 342 F.3d at 1330, 68 U.S.P.Q.2d at 1155 (emphasis added). Similarly, Appellants claims recite, "*A method of treating* seborrheic dermatitis *in a human patient in need thereof* comprising *administering to the patient* an amount effective for the treatment of seborrheic dermatitis of a composition . . . ." Claim 38 (emphasis added). The Federal Circuit held that the claim language at issue in *Jansen* must be interpreted to read on the treatment of a disease, not on treatment of mere symptoms. *Jansen,* 342 F.3d at 1333, 68 U.S.P.Q.2d at 1157-58.

To enforce the idea that treating symptoms does not equate to treating diseases, the *Jansen* panel pointed to a similar case, *Rapoport v. Dement*, 254 F.3d 1053, 59 U.S.P.Q.2d (BNA) 1215 (Fed. Cir. 2001):

> On appeal [in *Rapoport*] we gave weight to the ordinary meaning of the preamble phrase "for treatment of sleep apneas," interpreting it to refer to sleep apnea, *per se*, not just "symptoms associated with sleep apnea." Rapoport argued that the count was unpatentable on the ground that a prior art reference disclosed that a form of the compound recited in the claim could be administered, not for treatment of sleep apnea itself, but for treatment of anxiety and breathing difficulty, a symptom of apnea. We rejected that argument, stating, "There is no disclosure in the [prior art reference that the compound] is administered to patients suffering from sleep apnea *with the intent to cure the underlying condition.*" Thus, the claim was interpreted to require that the method be practiced with the intent to achieve the objective stated in the preamble.

Jansen, 342 F.3d at 1333, 68 U.S.P.Q.2d at 1157-58 (*quoting Rapoport*, 254 F.3d at 1059 and 1061, 59 U.S.P.Q.2d at 1219 and 1221, *and adding emphasis*). As in *Jansen* and *Rapoport*, claims 38 and 39 recite "in need thereof," indicating treatment of SD itself. Also, as in *Jansen* and *Rapoport*, the amended claims do not explicitly recite "intent," but the preambles of the claims of *Jansen*, *Rapoport*, and the present application ought to be interpreted to exclude prior art that fails to reveal any intent to treat the underlying conditions just like the preambles in *Jansen* and *Rapoport*. Accordingly, the amended claims should be construed to require treatment of a human patient for the disease of seborrheic dermatitis, and not just a symptom associated with the disease.

2. The Combination of *Verdicchio*, *Janniger* and *Dittmar* Does Not Render Claims 38-42, 48, and 61-66 Obvious

The Examiner applies *Verdicchio* and *Janniger* as described above and reasons that the rejected claims would have been obvious "because both dandruff and seborrheic dermatitis are produced by the same causative agent, *Pityrosporum ovale*, and is generally treated using the same types of medicinal shampoo (e.g., see Janniger et al. . . .)" Final Office Action at 32 and 33; *see also* Advisory Action at 29. Thus, the Examiner concludes, "it would be prima facie obvious to treat the 'separate' seborrheic dermatitis condition with dandruff shampoo like the dandruff shampoo set forth in Verdicchio." *Id.* at 33; *see also* Advisory Action at 29. The skilled artisan would allegedly have had a reasonable expectation of success because, according to the Examiner, both dandruff and seborrheic dermatitis "are produced from a common microbe, *Pityrosporum ovale* organism." *Id*; *see also* Advisory Action at 29. The Examiner bases a motivation to combine in the alleged teaching in *Dittmar* that "pyridones can be used as 'anti-seborrheic' agents.'" *Id.*; *see also* Advisory Action at 29. Appellants again disagree.

The Examiner also suggests that "oily skin plays a big role in seborrheic dermatitis as exemplified by the word 'seborrhea' which means 'too much oil.'" Advisory Action at 31. Based on this unsupported assertion, the Examiner concludes that "a person of ordinary skill in the art would be motivated to use agents that treat oily skin against seborrheic dermatitis whether such treatments constituted a formalistic treatment of seborrheic dermatitis or not." *Id.*

Appellants note that "seborrhea" (as used in "anti-seborrheic") is not the same as SD. Seborrhea refers to the oil (sebum) of the skin and "anti-seborrheic agents" are used to combat oily skin. SD is a separate disorder, which involves the hyperproliferation of keratinocytes and inflammation. See Leyden declaration at 2; see also Section VII.B.2 above. Therefore, the Examiner incorrectly equates "anti-seborrheic agents" with SD treatments: to the contrary, the terms refer to two separate disorders.

Further, the Examiner's foundation for this obviousness rejection is the perception that dandruff and SD are caused by the same organism. But, as Appellant has explained, at the time of the invention, it was unclear to persons of ordinary skill in the pertinent art as to what causes SD. See Reply filed June 4, 2007, at 23 and 24. A hypothesis that "favored an etiology involving bacteria, yeasts, or both ... has remained unsupported." Dermatology in General Medicine, 5th ed., page 2 of 17 (filed as Appendix A of the Wortzman declaration). Some in the art argue that "*P. ovale* is not the causative organism but is merely present in large numbers." *Id.* Other possible causes of seborrheic dermatitis include drugs, neuralgic abnormalities that affect the nervous system, physical factors such as temperature and humidity and nutritional disorders. *Id.* Moreover, *Lange* also instructs that "although yeast cells like Pityrosporum ovale . . . are normally found on the skin, some people do have dandruff while others don't." *Lange* at 1, third paragraph. This teaching argues against *P. ovale* being the causative agent of dandruff because it is not specifically associated with incidents of dandruff.

According to the Examiner, the "best scientific data" indicates that P. ovale is responsible for both dandruff and SD. Advisory Action at 30. However, Appellants have provided evidence from *Lange* and from one of ordinary skill in the art, Dr. Wortzman, who has a Ph.D. in cellular and molecular biology and has been involved in research and development for numerous dermatological products, that there are contrary teachings that do not suggest that *P. ovale* is the cause. Indeed, the Examiner acknowledges that there is "no definitive proof" on the point of whether *P. ovale* causes both dandruff and SD, thus contradicting his own statements in support of the rejection. *Id.*

With regard to *Dittmar*, the Examiner disagrees with Appellants' argument that *Dittmar* teaches away from the claimed invention because *Dittmar* provides a list of additional components that can be used with 1-hydroxy-2-pyridone. Advisory Action at 31. The Examiner contends that there is no teaching away because *Dittmar* does not teach that the invention "will not work" unless multiple ingredients are used. *Id.* A teaching that other additives can be added to the active ingredient coupled with the assumption that the more active ingredients a product has, the more effective it is, a reasonable assumption for the skilled artisan to make, teaches away from a sole active ingredient as recited in the claims.

Because it is unclear what causes the different conditions of dandruff and SD, the Examiner's basis for an expectation of success falls. Indeed, as Appellant has explained, there are significant differences between the symptoms of dandruff and SD. Based on what a person of ordinary skill in the pertinent art would have known at the time of the invention, the skilled artisan would not have reasonably expected to have

been able to use a dandruff treatment as a treatment for SD. The conditions are two different conditions and the cause of each condition was not established in the art at the time of the invention, as demonstrated by, for example, *Lange*'s teaching. Because the Examiner has not shown that claims 38-42, 48, and 61-66 are anticipated or obvious, the Board should reverse this rejection.

F. Provisional Rejection of Claims 38-42, 48, and 61-66 Under the Judicially Created Doctrine of Obviousness-type Double Patenting Over claims 14-23 and 26-29 of U.S. Application No. 10/606,229

The Examiner provisionally rejects claims 38-42, 48, and 61-66 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 14-23 and 26-29 of copending application number 10/606,229. Final Office Action at 27; see also Advisory Action at 32. According to the Examiner, the claims in both applications are "drawn to the same treatment of seborrheic dermatitis using the same 1-hydroxy-2-pyridone compounds having the same generic formula. *Id.*; see also Advisory Action at 32.

Because this rejection is a provisional rejection and no patentable subject matter has yet been identified in copending application number 10/606,229, Appellants have not yet filed a Terminal Disclaimer in response to this rejection. Appellants note that the '229 application is currently under appeal and thus the final disposition and form of those claims is uncertain. If, however, patentable subject matter is identified in the '229 application, Appellants will file a Terminal Disclaimer in the instant application to obviate this rejection. Nonetheless, at this time, Appellants request removal of this rejection upon allowance of the present claims.

CONCLUSION

For the reasons given above, pending claims 38-42, 48, and 61-66 are allowable, and Appellants respectfully request reversal of the outstanding rejections.

Authorization of Deposit Account

The Commissioner is hereby authorized to charge any fees which may be required during the entire pendency of this application, or credit any overpayment, to Deposit Account 18-0586. This authorization also hereby includes a request for any extensions of time of the appropriate length required upon the filing of any reply during the entire pendency of this application.

CERTIFICATE OF MAILING UNDER 37 C.F.R. 1.10

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Cody M. Nye
(Name of person mailing paper.)

(Signature of person mailing paper.)

Respectfully submitted,
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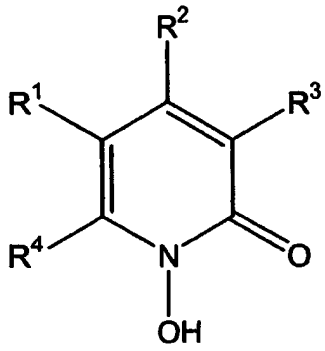
VIII. Claims Appendix

1-37. (Canceled).

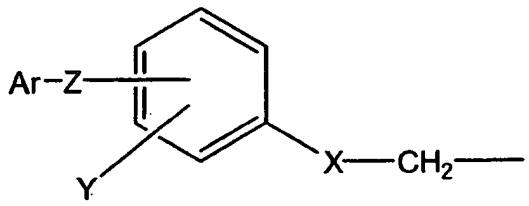
38. A method of treating seborrheic dermatitis in a human patient in need thereof comprising administering to the patient an amount effective for the treatment of seborrheic dermatitis of a single composition, wherein this composition comprises:

(A) a sole active component, which is a 1-hydroxy-2-pyridone of formula I or a pharmaceutically acceptable salt thereof:



(I)

where R^1, R^2, and R^3, which are identical or different, are H or alkyl having 1 to 4 carbon atoms, and R^4 is a saturated hydrocarbon radical having 6 to 9 carbon atoms or a radical of formula II:



(II)

where:

X is S or O;

Y is H, or 1 or 2 identical halogen atoms, or a mixture of 2 different halogen atoms;

Z is a single bond, or

a linking radical comprising

(1) O, or

(2) S, or

(3) $-CR_2-$, where R is H or (C_1-C_4)-alkyl, or

(4) from 2 to 10 carbon atoms linked in the form of a straight or branched chain, which optionally further comprises one or more of the following:

(i) a carbon-carbon double bond, and

(ii) O, S, or a mixture thereof, wherein if 2 or more O or S atoms or a mixture thereof are present, each O or S atom is separated by at least 2 carbon atoms; and,

in any of the foregoing linking radicals, any remaining free valences of the carbon atoms of said linking radical are saturated by H, (C_1-C_4)-alkyl, or a mixture thereof;

and

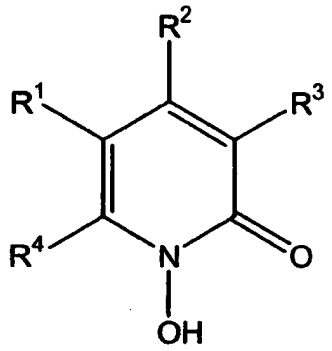
Ar is an aromatic ring system having one or two rings, the aromatic ring system being unsubstituted or substituted by one, two, or three radicals, which are identical or different, and are chosen from halogen, methoxy, (C_1-C_4)-alkyl, trifluoromethyl, and trifluoromethoxy; and

(B) at least one surfactant chosen from anionic surfactants, cationic surfactants, nonionic surfactants, and amphoteric surfactants; and

wherein the composition has a pH ranging from about 4.5 to about 6.5.

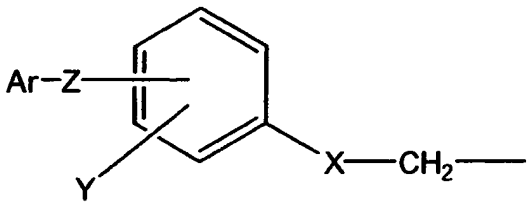
39. A method of treating seborrheic dermatitis in a human patient in need thereof comprising administering to the patient an amount effective for the treatment of seborrheic dermatitis of a single composition, wherein this composition comprises:

(A) a sole active component, which is a 1-hydroxy-2-pyridone of formula I or a pharmaceutically acceptable salt thereof:



(I)

where R^1, R^2, and R^3, which are identical or different, are H or alkyl having 1 to 4 carbon atoms, and R^4 is a saturated hydrocarbon radical having 6 to 9 carbon atoms or a radical of formula II:



(II)

where:

X is S or O;

Y is H, or 1 or 2 identical halogen atoms, or a mixture of 2 different halogen atoms;

Z is a single bond, or

a linking radical comprising

(1) O, or

(2) S, or

(3) $-CR_2-$, where R is H or (C_1-C_4)-alkyl, or

(4) from 2 to 10 carbon atoms linked in the form of a straight or branched chain, which optionally further comprises one or more of the following:

(i) a carbon-carbon double bond, and

(ii) O, S, or a mixture thereof, wherein if 2 or more O or S atoms or a mixture thereof are present, each O or S atom is separated by at least 2 carbon atoms; and,

in any of the foregoing linking radicals, any remaining free valences of the carbon atoms of said linking radical are saturated by H, (C_1-C_4)-alkyl, or a mixture thereof;

and

Ar is an aromatic ring system having two rings, the aromatic ring system being unsubstituted or substituted by one, two, or three radicals, which are identical or different, and are chosen from halogen, methoxy, (C_1-C_4)-alkyl, trifluoromethyl, and trifluoromethoxy, and wherein Ar is a bicyclic system derived from biphenyl, diphenylalkane, or diphenyl ether; and

(B) at least one surfactant chosen from anionic surfactants, cationic surfactants, nonionic surfactants, and amphoteric surfactants.

40. A method of treating seborrheic dermatitis in a human patient in need thereof as claimed in claim 38 in which the at least one 1-hydroxy-2-pyridone of formula I has a cyclohexyl radical in the R^4 position.

41. A method of treating seborrheic dermatitis in a human patient in need thereof as claimed in claim 38 in which the at least one 1-hydroxy-2-pyridone of formula I has an octyl radical of the formula $-CH_2-CH(CH_3)-CH_2-C(CH_3)_3$ in the R^4 position.

42. A method of treating seborrheic dermatitis in a human patient in need thereof as claimed in claim 38 in which the sole active component is 1-hydroxy-4-methyl-6-(4-(4-chlorophenoxy)phenoxymethyl)-2(1H)pyridone, 1-hydroxy-4-methyl-6-cyclohexyl-2(1H)pyridone, or 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1H)pyridone, or a pharmaceutically acceptable salt of any of the foregoing.

43-47. (Canceled).

48. A method of treating seborrheic dermatitis in a human patient in need thereof as claimed in claim 38 in which the composition further comprises at least one additional surfactant chosen from anionic, cationic, nonionic, and amphoteric surfactants.

49-60. (Canceled).

61. A method of treating seborrheic dermatitis in a human patient in need thereof as claimed in claim 39 in which the at least one 1-hydroxy-2-pyridone of formula I has a cyclohexyl radical in the R^4 position.

62. A method of treating seborrheic dermatitis in a human patient in need thereof as claimed in claim 39 in which the at least one 1-hydroxy-2-pyridone of formula I has an octyl radical of the formula $-CH_2-CH(CH_3)-CH_2-C(CH_3)_3$ in the R^4 position.

63. A method of treating seborrheic dermatitis in a human patient in need thereof as claimed in claim 39 in which the sole active component is 1-hydroxy-4-methyl-6-(4-(4-chlorophenoxy)phenoxymethyl)-2(1H)pyridone, 1-hydroxy-4-methyl-6-cyclohexyl-2(1H)pyridone, or 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1H)pyridone, or a pharmaceutically acceptable salt of any of the foregoing.

64. A method of treating seborrheic dermatitis in a human patient in need thereof as claimed in claim 39 in which the composition further comprises at least one additional surfactant chosen from anionic, cationic, nonionic, and amphoteric surfactants.

65. A method of treating seborrheic dermatitis in a human patient in need thereof as claimed in claim 38, in which the sole active component is a pharmaceutically acceptable salt of a 1-hydroxy-2-pyridone of formula I, and in which the composition

further comprises lactic acid to adjust the pH of the composition to the pH ranging from about 4.5 to about 6.5.

66. A method of treating seborrheic dermatitis in a human patient in need thereof as claimed in claim 39, in which the composition further comprises lactic acid to adjust the pH of the composition.

67. (Canceled).

IX. Evidence Appendix

Declaration of R. Todd Plott, M.D., dated July 17, 2006	Tab 1
Declaration of James Leyden, M.D., dated January 4, 2006	Tab 2
Declaration of Mitchell S. Wortzman, Ph.D., dated June 6, 2003	Tab 3

1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Reissue Patent Application of:
Bohn

Appln. Nos.: 09/077,194 and 10/606,229

Filing Date: December 4, 1998 and June 26, 2003

Title: USE OF 1-HYDROXY-2-PYRIDONES FOR THE TREATMENT OF SEBORRHEIC DERMATITIS

DECLARATION OF R. TODD PLOTT, M.D. UNDER 37 C.F.R. § 1.132

I, R. Todd Plott, M.D., being of legal age, declare as follows.

1. I am Vice President for Clinical Research and Regulatory Affairs of Medicis Pharmaceutical Corporation ("Medicis"). I am also a board certified dermatologist.

2. I received my undergraduate degree in Biology/Chemistry and History from Bethany Nazarene College and my M.D. from University of Texas Medical Branch in Galveston, Texas. My internship and residency in dermatology was at the University of Arkansas of Medical Sciences. My fellowship in dermatology was at the National Institutes of Health, National Cancer Institute.

3. After my fellowship, I was employed by Hoechst Roussel Pharmaceuticals and then Rhone-Poulenc Rorer Company (Dermik Laboratories, Inc.) as Director of Clinical Research. I then became Director, Worldwide Clinical Development for Galderma Laboratories, Inc. Then I was Director, Clinical Research in Dermatology and Anti-Infectives/Dermatology for Schering-Plough Research Institute. My employment at Medicis began in 2001. As can be seen, I have had significant experience in product development and clinical research in the field of dermatological products.

4. As Vice President of Medicis, my responsibilities include oversight of the development of new dermatological drug products, and of the preparation of applications for regulatory approval by the U.S. Food & Drug Administration.

Brochure

5. I am familiar with the brochure prepared by Medicis, which is attached hereto as Exhibit A.

6. This brochure was prepared in part to educate physicians (especially those who are not dermatologists) about seborrheic dermatitis.

7. The brochure points out that seborrheic dermatitis is sometimes confused with dandruff. While non-dermatologist physicians sometimes make this mistake, dermatologists know that seborrheic dermatitis is an inflammatory disorder associated with the hyperproliferation of keratinocytes, while dandruff is a "noninflammatory" scaling of the scalp. While both disorders can include flaking skin among their symptoms, they are known by dermatologists to be different disorders.

8. This brochure points out that non-dermatologists are sometimes unaware of this distinction. (See p. 2, where the brochure mentions "mistaken.")

9. Medicis no longer uses this brochure because, among other reasons, parts of it are not sufficiently clear and could be taken to confuse the distinction between these two disorders.

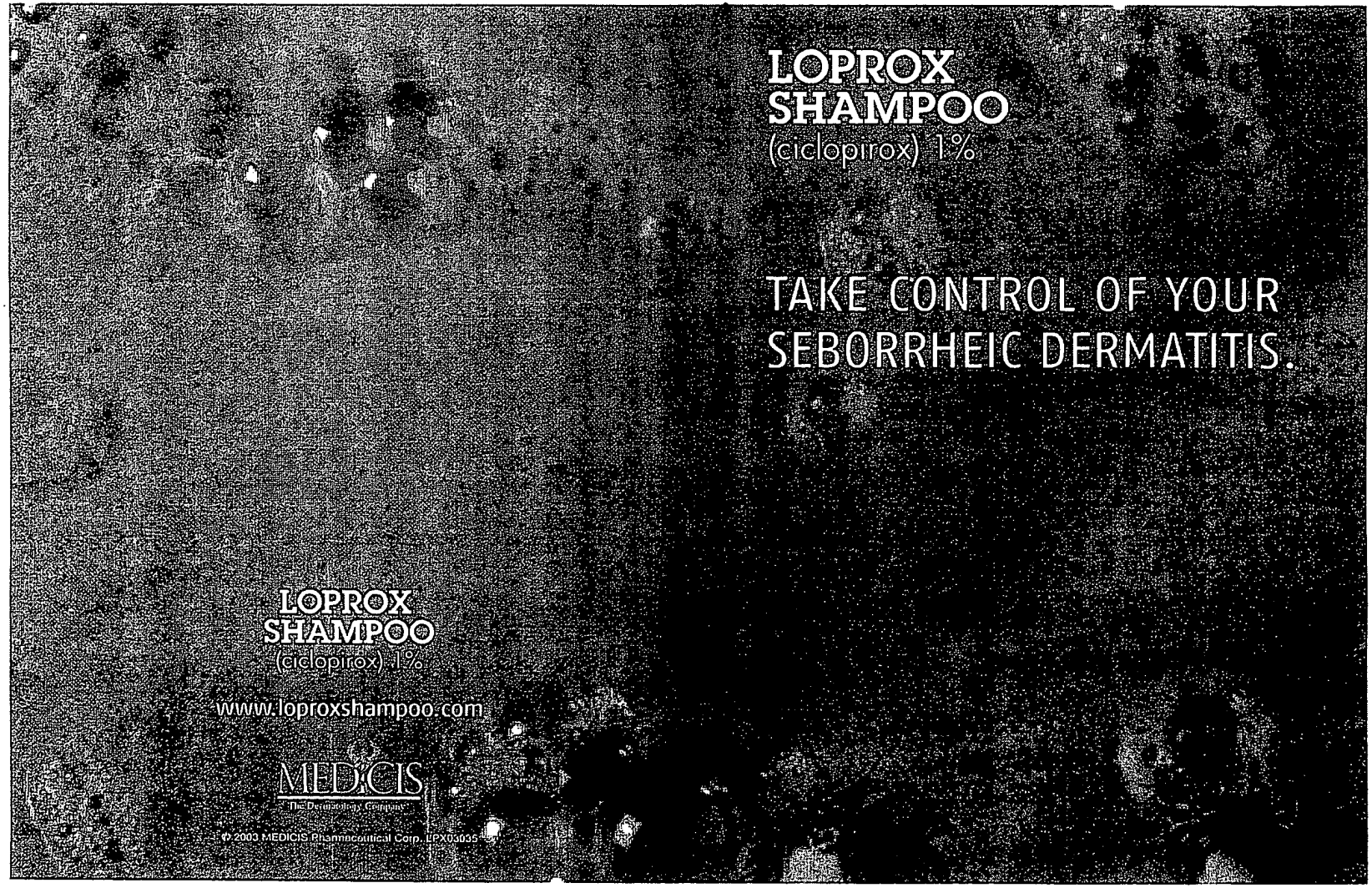
10. This brochure also mistakes a common secondary infection associated with seborrheic dermatitis for a causative factor. "Seborrheic dermatitis of the scalp is a long-term condition that is thought to be caused by the overgrowth of a common fungus that naturally occupies the skin." While there may be secondary fungal infections, seborrheic dermatitis is not now thought to be caused by overgrowth of a fungus. I make this statement based upon my dermatology experience and work in this area.

All statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application and any registration resulting therefrom.

Date: 7/17/06

R. Todd Plott, M.D.

EXHIBIT A


LOPROX
SHAMPOO
(ciclopirox) 1%
TAKE CONTROL OF YOUR
SEBORRHEIC DERMATITIS.
LOPROX
SHAMPOO
(ciclopirox) 1%
www.loproxshampoo.com
MEDICIS
"The Dermatology Company"
© 2003 MEDICIS Pharmaceutical Corp. LPX03035

What is seborrheic dermatitis of the scalp?

Seborrheic dermatitis of the scalp is an embarrassing, sometimes itchy and flaky condition. It is a common condition that affects about 3% of the general population[1]. It is frequently mistaken for dandruff, which is considered a mild form of seborrheic dermatitis.

The signs and symptoms of seborrheic dermatitis include greasy flaking, scaling, redness, itching, and burning of the scalp. Like dandruff, seborrheic dermatitis is a chronic condition that will persist and become more severe unless properly treated. Those who suffer from seborrheic dermatitis of the scalp are affected in multiple ways, from physical discomfort to awkward social situations. For example, many sufferers must avoid wearing dark clothing, fearful that their flakes will draw unwanted attention to their condition.

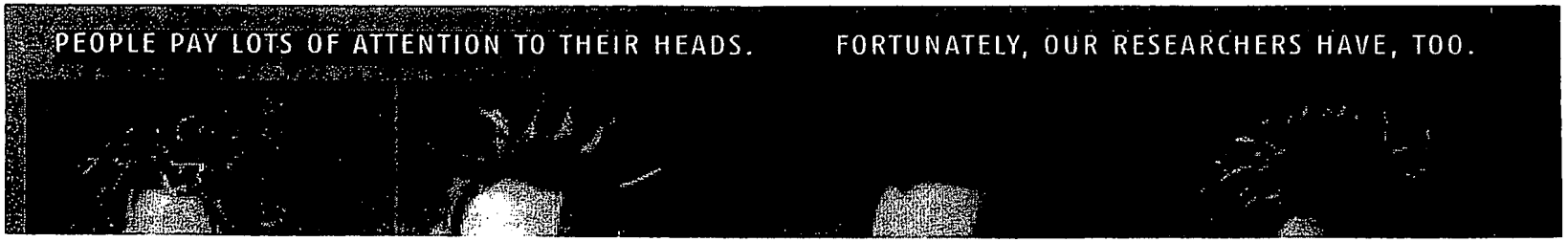
While seborrheic dermatitis is a chronic condition and cannot be prevented or cured, it can be effectively managed with ongoing treatment.

What causes seborrheic dermatitis of the scalp?

Seborrheic dermatitis of the scalp is a long-term condition that is thought to be caused by the overgrowth of a common fungus that naturally occupies the skin. It is normal for this fungus to be present and it is not contagious. It is not related to personal hygiene or how often you wash your hair.

Although seborrheic dermatitis of the scalp most often occurs in people between the ages of 20-50, this condition usually starts during puberty[2]. Seborrheic dermatitis of the scalp can also affect infants[3]. Most people with seborrheic dermatitis are otherwise healthy. However, people who also have rosacea, psoriasis, or severe acne are more likely to also have seborrheic dermatitis of the scalp[2-4].

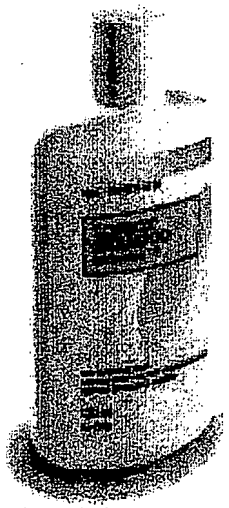
Scratching, changes in humidity, and physical or emotional stress may cause your condition to worsen. Seasonal changes can also affect your condition, making it more severe in winter and early spring, and less severe in summer.



What is LOPROX® Shampoo?

LOPROX Shampoo is the first and only antifungal shampoo specifically approved for seborrheic dermatitis of the scalp in adults.[1] LOPROX Shampoo works well because it focuses directly on the source of the problem—the fungus that may cause seborrheic dermatitis.

Because this condition can increase the sensitivity of your scalp, a non-irritating treatment will be needed. LOPROX Shampoo is a gentle formulation, free of fragrance and dye.[1] It safely and effectively treats the area without harsh ingredients. In fact, more than 97% of users experience no negative effects.[1]



Available by prescription only, LOPROX is a name trusted by dermatologists for more than 20 years.

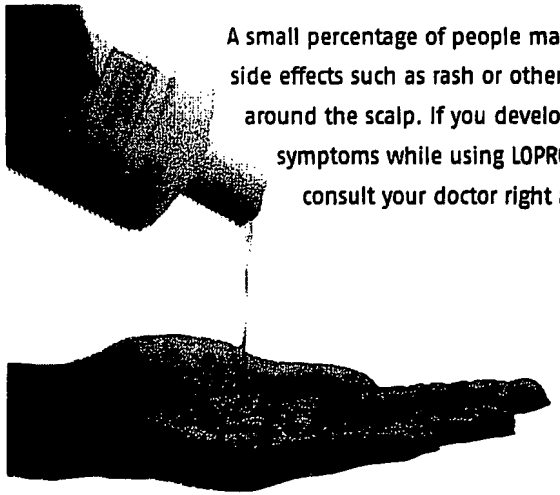
The most common adverse reactions reported are pruritus (itching), burning, erythema (redness), seborrhea, and rash.

How do I use LOPROX® Shampoo?

LOPROX Shampoo should be used at least twice weekly, or as often as prescribed by your doctor.

Make LOPROX Shampoo a simple part of your weekly routine. On the days that you use LOPROX Shampoo, you do not need to use your regular shampoo. For best results, leave the rich, foamy lather of LOPROX Shampoo on your hair and scalp for 3 minutes before rinsing.

Seborrheic dermatitis is a chronic condition, so continued use is important. Be sure to have your prescription refilled as often as directed by your doctor. If used regularly, LOPROX Shampoo can help you keep your condition under control.

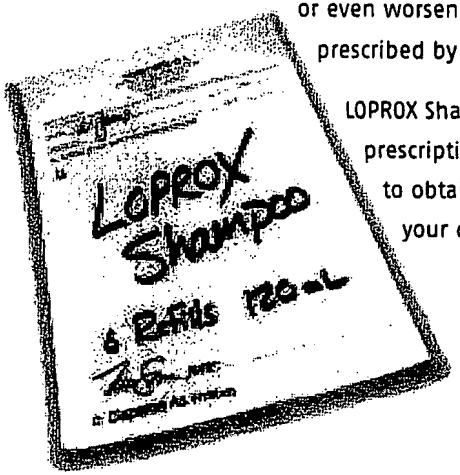


A small percentage of people may experience side effects such as rash or other discomfort around the scalp. If you develop any of these symptoms while using LOPROX Shampoo, consult your doctor right away.

What can I expect?

You should begin to notice results in as soon as two to four weeks of regular use? Seborrheic dermatitis is a chronic condition, and LOPROX Shampoo can help you to conveniently and comfortably manage it.

Without regular treatment, seborrheic dermatitis can reappear without warning. Your doctor may direct you to continue using LOPROX shampoo even after symptoms improve. Stopping treatment early may not clear your condition, allowing it to return or even worsen. Continue use as prescribed by your doctor.



LOPROX Shampoo is available by prescription only, so remember to obtain refills as directed by your doctor.

The most common adverse reactions reported are pruritus (itching), burning, erythema (redness), seborrhea, and rash.

Diary

Please check or rate the following as indicated

Week of _____	LOPROX® Shampoo ✓	Improvement of Seborrheic Dermatitis 1 (high) to 5 (low) 1-5	Comments (areas affected) Fill in
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			
Week of _____	✓	1-5	Fill in
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

Diary

Please check or rate the following as indicated

Week of _____	LOPROX® Shampoo ✓	Improvement of Seborrheic Dermatitis 1 (high) to 5 (low) 1-5	Comments (areas affected) Fill in
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

Week of _____	✓	1-5	Fill in
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

Diary

Please check or rate the following as indicated

Week of _____	LOPROX® Shampoo ✓	Improvement of Seborrheic Dermatitis 1 (high) to 5 (low) 1-5	Comments (areas affected) Fill in
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

Week of _____	✓	1-5	Fill in
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

Diary

Please check or rate the following as indicated

Week of _____	LOPROX® Shampoo ✓	Improvement of Seborrheic Dermatitis 1 (high) to 5 (low) 1-5	Comments (areas affected) Fill in
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			
Week of _____	✓	1-5	Fill in
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

References:

1. Moschella SL, Hurley HJ. The Other Eczemas: Seborrheic Dermatitis. Dermatology. WB Saunders Company, Philadelphia; 1992:1:466.
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4. Champion RH, Burton JL, Ebling FJG. Psoriasis Textbook of Dermatology 5th Ed. Blackwell Scientific Publications, Oxford; 1992:2:1412.
5. *Physicians' Desk Reference* 2003.
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8. Elewski BE. Pityrosporum Infections: Seborrheic Dermatitis. Cutaneous Fungal Infections. Blackwell Science, Inc. Malden; 1998: 79.
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LOPROX® SHAMPOO
(ciclopirox) 1%

Rx Only
FOR TOPICAL USE ONLY
NOT FOR OPHTHALMIC, ORAL OR INTRAVAGINAL USE
KEEP OUT OF REACH OF CHILDREN

DESCRIPTION

LOPROX® (ciclopirox) Shampoo 1% contains the synthetic antifungal agent, ciclopirox.

Each gram (equivalent to 0.96 ml) of LOPROX Shampoo contains 10 mg ciclopirox in a shampoo base consisting of Purified Water USP, Sodium Laureth Sulfate, Disodium Laureth Sulfosuccinate, Sodium Chloride USP, and Laureth-2.

LOPROX Shampoo is a colorless, translucent solution. The chemical name for ciclopirox is 6-cyclohexyl-1-hydroxy-4-methyl-2(1*H*)-pyridone, with the empirical formula $C_{12}H_{17}NO_2$ and a molecular weight of 207.27. The CAS Registry Number is [29342-05-0]. The chemical structure is:

CLINICAL PHARMACOLOGY

Mechanism of Action

Ciclopirox is a hydroxypyridone antifungal agent although the relevance of this property to the indication of seborrheic dermatitis is not known. Ciclopirox acts by chelation of polyvalent cations (Fe^{3+} or Al^{3+}), resulting in the inhibition of the metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cell.

Pharmacokinetics and Pharmacodynamics

In a study in patients with seborrheic dermatitis of the scalp, application of 5 ml ciclopirox shampoo 1% twice weekly for 4 weeks, with an exposure time of 3 minutes per application, resulted in detectable serum concentrations of ciclopirox in 6 out of 18 patients. The serum concentrations measured throughout the dosing interval on Days 1 and 29 ranged from 10.3 ng/ml to 13.2 ng/ml. Total urinary excretion of ciclopirox was less than 0.5% of the administered dose.

CLINICAL STUDIES

In two randomized, double-blind clinical trials, patients 16 years and older with seborrheic dermatitis of the scalp applied LOPROX Shampoo or its vehicle two times per week for 4 weeks. Patients who were immunocompromised, those with psoriasis or atopic dermatitis, women of childbearing potential not using adequate contraception, and pregnant or lactating women were excluded from the clinical studies. An evaluation of the severity status of the seborrheic dermatitis, and the presence and severity of erythema or inflammation, and scaling, was made at week 4, using a scale of 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = pronounced, and 5 = severe. Effective treatment was defined as achieving a score of 0 (or a score of 1 if the baseline score was ≥ 3) simultaneously for both of the seborrheic dermatitis, erythema or inflammation, and scaling at Week 4. Ciclopirox shampoo was shown to be statistically significantly more effective than vehicle in both studies. Efficacy results for the two studies are presented in the following table.

Effective Treatment Rates at Week 4 in Studies 1 and 2

	Ciclopirox Shampoo	Vehicle
Study 1	220/380 (58%)	60/192 (31%)
Study 2	65/250 (26%)	32/249 (13%)

Efficacy for black patients was not demonstrated, although only 53 black patients were enrolled in the two pivotal studies.

Microbiology

Ciclopirox is fungicidal *in vitro* against *Malassezia furfur (Pityrosporum spp.), P. ovale,* and *P. orbiculare*. Ciclopirox acts by chelation of polyvalent cations (Fe^{3+} or Al^{3+}), resulting in the inhibition of the metal dependent enzymes that are responsible for the degradation of peroxides within the fungal cell.

The clinical significance of antifungal activity in the treatment of seborrheic dermatitis is not known.

INDICATIONS AND USAGE

LOPROX Shampoo is indicated for the topical treatment of seborrheic dermatitis of the scalp in adults.

CONTRAINDICATIONS

LOPROX Shampoo is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS

LOPROX Shampoo is not for ophthalmic, oral, or intravaginal use.

Keep out of reach of children.

PRECAUTIONS

General

If a reaction suggesting sensitivity or irritation should occur with the use of LOPROX Shampoo, treatment should be discontinued and appropriate therapy instituted.

Contact of LOPROX Shampoo with the eyes should be avoided. If contact occurs, rinse thoroughly with water.

Seborrheic dermatitis may appear at puberty, however, no clinical studies have been done in patients younger than 16 years.

There is no relevant clinical experience with patients who have a history of immunosuppression (e.g., extensive, persistent, or unusual distribution of dermamycoses, recent or recurring herpes zoster, or persistent herpes simplex), who are immunocompromised (e.g., HIV infected patients and transplant patients), or who have a diabetic neuropathy.

Information for Patients

The patient should be instructed to:

1. Use LOPROX Shampoo as directed by the physician. Avoid contact with the eyes and mucous membranes. If contact occurs, rinse thoroughly with water. LOPROX Shampoo is for external use on the scalp only. Do not swallow.
2. Use the medication for seborrheic dermatitis for the full treatment time even though symptoms may have improved. Notify the physician if there is no improvement after 4 weeks.
3. Inform the physician if the area of application shows signs of increased irritation (redness, itching, burning, blistering, swelling, or cracking) indicative of possible allergic reaction.
4. Not use the medication for any disorder other than that for which it is prescribed.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of LOPROX Shampoo or ciclopirox.

The following *in vitro* genotoxicity tests have been conducted with ciclopirox: evaluation of gene mutation in the Ames *Salmonella* and *E. coli* assays (negative); chromosome aberration assays in V79 Chinese hamster lung fibroblast cells, with and without exogenous metabolic activation (positive); chromosome aberration assays in V79 Chinese hamster lung fibroblast cells in the presence of supplemented Fe^{3+}, with and without metabolic activation (negative); gene mutation assays in the HGPRTase with V79 Chinese hamster lung fibroblast cells (negative), and a primary DNA damage assay (i.e., unscheduled DNA synthesis assay in A549 human cells) (negative). An *in vitro* cell transformation assay in BALB/c 3T3 cells was negative for cell transformation. In an *in vivo* Chinese hamster bone marrow cytogenetic assay, ciclopirox was negative for chromosome aberrations at a dosage of 5000 mg/kg body weight.

A combined oral fertility and embryotoxic developmental study was conducted in rats with ciclopirox olamine. No effect on fertility or reproductive performance was noted at the highest dose tested of 2.85 mg/kg/day ciclopirox (approximately 1.3 times the maximum recommended human dose based on body surface area comparisons).

Pregnancy

Teratogenic effects: Pregnancy Category B

Oral embryotoxic developmental studies were conducted in mice, rats, rabbits and monkeys. Ciclopirox or ciclopirox olamine was orally administered during the period of organogenesis. No maternal toxicity, embryotoxicity or teratogenicity were noted at the highest doses of 77, 125, 80 and 38.5 mg/kg/day ciclopirox in mice, rats, rabbits and monkeys, respectively (approximately 13, 42, 54 and 26 times the maximum recommended human dose based on body surface area comparisons, respectively).

Dermal embryotoxic developmental studies were conducted in rats and rabbits with ciclopirox olamine dissolved in PEG 400. Ciclopirox olamine was topically administered during the period of organogenesis. No maternal toxicity, embryotoxicity or teratogenicity were noted at the highest doses of 92 mg/kg/day and 77 mg/kg/day ciclopirox in rats and rabbits, respectively (approximately 31 and 54 times the maximum recommended human dose based on body surface area comparisons, respectively).

There are no adequate or well-controlled studies of topically applied ciclopirox in pregnant women. Because animal reproduction studies are not always predictive of human response, LOPROX Shampoo should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when LOPROX Shampoo is administered to a nursing woman.

Pediatric Use

Seborrheic dermatitis may appear at puberty, however, no clinical studies have been done in patients younger than 16 years.

Geriatric Use

In clinical studies, the safety and tolerability of LOPROX Shampoo in the population 65 years and older was comparable to that of younger subjects. Results of the efficacy analysis in those patients 65 years and older showed effectiveness in 25 of 83 (29%) patients treated with LOPROX Shampoo, and in 15 of 61 (25%) patients treated with the vehicle; due to the small sample size, a statistically significant difference was not demonstrated. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects, but greater sensitivity to adverse effects in some older individuals cannot be ruled out.

ADVERSE REACTIONS

In 626 patients treated with LOPROX Shampoo twice weekly in the two pivotal clinical studies, the most frequent adverse events were pruritus/stinging in 1% of patients, and application site reactions, such as burning, erythema, and itching, also in 1% of patients. Other adverse events occurred in individual patients only.

Adverse events that led to early study medication termination in clinical trials occurred in 1.5% (9/626) of patients treated with LOPROX Shampoo and 2.0% (12/661) of patients treated with shampoo vehicle. The most common adverse events leading to discontinuation of study medication in either group was seborrhea. In the LOPROX Shampoo group, other adverse events included rash, pruritus, headache, ventricular tachycardia, and skin disorder. In the shampoo vehicle group, other adverse events included skin disorder and rash.

DOSAGE AND ADMINISTRATION

Wet hair and apply approximately 1 teaspoon (5 ml) of LOPROX Shampoo to the scalp. Up to 2 teaspoons (10 ml) may be used for long hair. Lather and leave on hair and scalp for 3 minutes. A timer may be used. Avoid contact with eyes. Rinse off. Treatment should be repeated twice per week for 4 weeks, with a minimum of 3 days between applications.

If a patient with seborrheic dermatitis shows no clinical improvement after 4 weeks of treatment with LOPROX Shampoo, the diagnosis should be reviewed.

HOW SUPPLIED

LOPROX® (ciclopirox) Shampoo 1% is supplied in 120 ml plastic bottles (NDC 99207-010-10). Discard unused product after initial treatment duration. Store between 15°C and 30°C (59°F and 86°F).

Manufactured for:
MEDICIS® Pharmaceutical Corp.
Scottsdale, AZ 85258
by: Patheon, Inc.
Mississauga, Ontario L5N 7K9
CANADA

PRESCRIBING INFORMATION AS OF FEBRUARY 2002

LOPROX® SHAMPOO
(ciclopirox) 1%

Rx Only
FOR TOPICAL USE ONLY
NOT FOR OPHTHALMIC, ORAL OR INTRAVAGINAL USE
KEEP OUT OF REACH OF CHILDREN

DESCRIPTION

LOPROX® (ciclopirox) Shampoo 1% contains the synthetic antifungal agent, ciclopirox.
Each gram (equivalent to 0.96 mL) of LOPROX Shampoo contains 10 mg ciclopirox in a shampoo base consisting of Purified Water USP, Sodium Laureth Sulfate, Disodium Laureth Sulfosuccinate, Sodium Chloride USP, and Laureth-2.
LOPROX Shampoo is a colorless, translucent solution. The chemical name for ciclopirox is 6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridone, with the empirical formula $C_{12}H_{17}NO_2$ and a molecular weight of 207.27. The CAS Registry Number is [29342-05-0]. The chemical structure is:

CLINICAL PHARMACOLOGY

Mechanism of Action

Ciclopirox is a hydroxypyridone antifungal agent although the relevance of this property for the indication of seborrheic dermatitis is not known. Ciclopirox acts by chelation of polyvalent cations (Fe^{3+} or Al^{3+}), resulting in the inhibition of the metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cell.

Pharmacokinetics and Pharmacodynamics

In a study in patients with seborrheic dermatitis of the scalp, application of 5 mL ciclopirox shampoo 1% twice weekly for 4 weeks, with an exposure time of 3 minutes per application, resulted in detectable serum concentrations of ciclopirox in 6 out of 18 patients. The serum concentrations measured throughout the dosing interval on Days 1 and 29 ranged from 10.3 ng/mL to 13.2 ng/mL. Total urinary excretion of ciclopirox was less than 0.5% of the administered dose.

CLINICAL STUDIES

In two randomized, double-blind clinical trials, patients 16 years and older with seborrheic dermatitis of the scalp applied LOPROX Shampoo or its vehicle two times per week for 4 weeks. Patients who were immunocompromised, those with psoriasis or atopic dermatitis, women of childbearing potential not using adequate contraception, and pregnant or lactating women were excluded from the clinical studies. An evaluation of the overall status of the seborrheic dermatitis, and the presence and severity of erythema or inflammation, and scaling, was made at week 4, using a scale of 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = pronounced, and 5 = severe. Effective treatment was defined as achieving a score of 0 (or a score of 1 if the baseline score was ≥ 3) simultaneously for status of the seborrheic dermatitis, erythema or inflammation, and scaling at Week 4. Ciclopirox shampoo was shown to be statistically significantly more effective than vehicle in both studies. Efficacy results for the two studies are presented in the following table.

Effective Treatment Rates at Week 4 in Studies 1 and 2

	Ciclopirox Shampoo	Vehicle
Study 1	220/380 (58%)	60/192 (31%)
Study 2	65/250 (26%)	32/249 (13%)

Efficacy for black patients was not demonstrated, although only 53 black patients were enrolled in the two pivotal studies.

Microbiology

Ciclopirox is fungicidal *in vitro* against *Malassezia furfur* (*Pityrosporum* spp.), *P. ovale*, and *P. orbiculare*. Ciclopirox acts by chelation of polyvalent cations (Fe^{3+} or Al^{3+}), resulting in the inhibition of the metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cell.
The clinical significance of antifungal activity in the treatment of seborrheic dermatitis is not known.

INDICATIONS AND USAGE

LOPROX Shampoo is indicated for the topical treatment of seborrheic dermatitis of the scalp in adults.

CONTRAINDICATIONS

LOPROX Shampoo is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS

LOPROX Shampoo is not for ophthalmic, oral, or intravaginal use.

Keep out of reach of children.

PRECAUTIONS

General

If a reaction suggesting sensitivity or irritation should occur with the use of LOPROX Shampoo, treatment should be discontinued and appropriate therapy instituted.
Contact of LOPROX Shampoo with the eyes should be avoided. If contact occurs, rinse thoroughly with water.
Seborrheic dermatitis may appear at puberty, however, no clinical studies have been done in patients younger than 16 years.
There is no relevant clinical experience with patients who have a history of immunosuppression (e.g., extensive, persistent, or unusual distribution of dermatomycoses, recent or recurring herpes zoster, or persistent herpes simplex), who are immunocompromised (e.g., HIV-infected patients and transplant patients), or who have a diabetic neuropathy.

Information for Patients

The patient should be instructed to:

1. Use LOPROX Shampoo as directed by the physician. Avoid contact with the eyes and mucous membranes. If contact occurs, rinse thoroughly with water. LOPROX Shampoo is for external use on the scalp only. Do not swallow.
2. Use the medication for seborrheic dermatitis for the full treatment time even though symptoms may have improved. Notify the physician if there is no improvement after 4 weeks.
3. Inform the physician if the area of application shows signs of increased irritation (redness, itching, burning, blistering, swelling, or oozing) indicative of possible allergic reaction.
4. Not use the medication for any disorder other than that for which it is prescribed.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Long-term animal studies have not been performed to evaluate the carcinogenic potential of LOPROX Shampoo or ciclopirox.

The following *in vitro* genotoxicity tests have been conducted with ciclopirox: evaluation of gene mutation in the Ames *Salmonella and E. coli* assays (negative); chromosome aberration assays in V79 Chinese hamster lung fibroblast cells, with and without metabolic activation (positive); chromosome aberration assays in V79 Chinese hamster lung fibroblast cells in the presence of supplemental Fe^{3+}, with and without metabolic activation (negative); gene mutation assays in the HGPRT-test with V79 Chinese hamster lung fibroblast cells (negative); and a primary DNA damage assay (i.e., unscheduled DNA synthesis assay in A549 human cells) (negative). An *in vitro* cell transformation assay in BALB/c 3T3 cells was negative for cell transformation. In an *in vivo* Chinese hamster bone marrow cytogenetic assay, ciclopirox was negative for chromosome aberrations at a dosage of 5000 mg/kg body weight.

A combined oral fertility and embryofetal developmental study was conducted in rats with ciclopirox olamine. No effect on fertility or reproductive performance was noted at the highest dose tested of 3.85 mg/kg/day ciclopirox (approximately 1.3 times the maximum recommended human dose based on body surface area comparisons).

Pregnancy:

Teratogenic effects: Pregnancy Category B

Oral embryofetal developmental studies were conducted in mice, rats, rabbits and monkeys. Ciclopirox or ciclopirox olamine was orally administered during the period of organogenesis. No maternal toxicity, embryotoxicity or teratogenicity were noted at the highest doses of 77, 125, 80 and 38.5 mg/kg/day ciclopirox in mice, rats, rabbits and monkeys, respectively (approximately 13, 42, 54 and 26 times the maximum recommended human dose based on body surface area comparisons, respectively).

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Seborrheic dermatitis may appear at puberty, however, no clinical studies have been done in patients younger than 16 years.

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In clinical studies, the safety and tolerability of LOPROX Shampoo in the population 65 years and older was comparable to that of younger subjects. Results of the efficacy analysis in those patients 65 years and older showed effectiveness in 25 of 85 (29%) patients treated with LOPROX Shampoo, and in 15 of 61 (25%) patients treated with the vehicle; due to the small sample size, a statistically significant difference was not demonstrated. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects, but greater sensitivity to adverse effects in some older individuals cannot be ruled out.

ADVERSE REACTIONS

In 626 patients treated with LOPROX Shampoo twice weekly in the two pivotal clinical studies, the most frequent adverse events were increased itching in 1% of patients, and application site reactions, such as burning, erythema, and itching, also in 1% of patients. Other adverse events occurred in individual patients only.

Adverse events that led to early study medication termination in clinical trials occurred in 1.5% (26/1738) of patients treated with LOPROX Shampoo and 2.0% (12/661) of patients treated with shampoo vehicle. The most common adverse events leading to termination of study medication in either group was seborrhea. In the LOPROX Shampoo group, other adverse events included rash, pruritus, headache, ventricular tachycardia, and skin disorder. In the shampoo vehicle group, other adverse events included skin disorder and rash.

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CANADA

PRESCRIBING INFORMATION AS OF FEBRUARY 2003

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Bohn, et al

Serial No. 10/606,229

Filing Date: June 26, 2003

USE OF 1-HYDROXY-2-PYRIDONES FOR THE TREATMENT OF SEBORRHEIC DERMATITIS

DECLARATION OF JAMES LEYDEN, M. D.

I, James Leyden, M.D., do hereby declare that:

1. My B.A. in Biology is from St Joseph's College (1962) and I obtained my M.D. from the University of Pennsylvania in 1966. I did my residency at the University of Pennsylvania.

2. I am a practicing dermatologist and have been so since 1972. I have held the following positions: Assistant, Associate Professor and Professor of Dermatology at the University of Pennsylvania, School of Medicine. I am currently an Emeritus Professor of Dermatology at the University of Pennsylvania, School of Medicine.

3. Over the years, I have authored numerous articles and books on dermatology, including several on the subject of scaling disorders of the scalp including the etiology of these disorders. My professional achievements include positions on the editorial boards of the Journal of the American Academy of Dermatology, and Skin and Aging among others and Editor-in-Chief of Cutaneous Aging and Cosmetic Dermatology. A copy of my CV is attached hereto as Exhibit A.

4. In my practice, I have treated numerous patients suffering from seborrhea and others suffering from seborrheic dermatitis. All of the following has been known to dermatologists since at least 1997.

5. Seborrhea is a condition of the sebaceous glands characterized by the excessive production of sebum by the sebaceous glands which, when it reaches the skin surface, makes the skin appear oily or shiny and feel greasy. Seborrhea does not involve the skin's keratinocytes, and does not cause seborrheic dermatitis.

6. Seborrheic dermatitis is not a condition of the sebaceous glands. *See* Fitzpatrick's Dermatology in General Medicine, 6th ed., p. 1198 (attached hereto as Exhibit B). It is a chronic papulosquamous dermatosis (*see* Ex. B, p. 1198), and a disorder characterized by the hyperproliferation of keratinocytes in the skin. It is characterized by erythema (redness of the skin), scaling and yellow crusted patches. See Ex. B, p. 1198-1199. The origin of the name, seborrheic dermatitis, is that the disorder is most prevalent in areas where there are high densities of sebaceous glands (e.g. face and ears), not because sebaceous glands, sebum or seborrhea are related to the disorder. Essentially, in seborrheic dermatitis, the epidermal keratinocytes multiply too quickly, causing scaling and other symptoms. The sebaceous glands are not involved in seborrheic dermatitis and excess sebum production is not a diagnostic feature of seborrheic dermatitis.

7. Seborrhea is not a subset of seborrheic dermatitis, nor is seborrheic dermatitis a subset of seborrhea. Seborrhea and seborrheic dermatitis are different disorders and involve different cells: the sebaceous glands (seborrhea) and the keratinocytes (seborrheic dermatitis).

8. It is well-known among dermatologists that not every seborrhea patient has seborrheic dermatitis. Conversely, it is well-known among dermatologists that not every seborrheic dermatitis patient has seborrhea. From my dermatology practice and years as a teacher and researcher in this field, it is apparent that seborrheic dermatitis is very common in older patients, most of whom do not have seborrhea. This would be known to any dermatologist. Fitzpatrick concurs stating, "an increased sebum production cannot always be detected in [seborrheic dermatitis] patients," and "seborrheic dermatitis is not a disease of the sebaceous glands." *See* Ex. B, p. 1198. Other treatises reflect this view.

9. U.S. Patent No. 4,172,149 (filed in 1978, and attached hereto as Exhibit C), states that seborrhea (or excessive sebum) is "one component of the pathology [of seborrheic dermatitis]." This is wrong. It does not reflect the understanding of practitioners in this field.

10. U.S. Patent No. 6,120,756 states that seborrheic dermatitis "as used herein is defined as chronic inflammatory disease of the skin associated with excessive sebum production," (Col. 6, Lines 30-32, attached hereto as Exhibit D.) While this patent may so define this term for its own purposes, that doesn't reflect the understanding of the art, i.e., it is wrong. *See* Ex. B. Seborrheic dermatitis is a chronic inflammatory disease of the keratinocytes but it is not associated with excessive sebum production. *See* Ex. B, p. 1198-1199. Many, if not most, patients with seborrheic dermatitis do not have excessive sebum production. In fact, there is no evidence that seborrheic dermatitis is associated with either increased or decreased sebum production.

11. Because seborrhea and seborrheic dermatitis are totally different disorders, a dermatologist would not normally use an anti-seborrheic agent (that is, an agent used to treat seborrhea) to treat seborrheic dermatitis. This is especially true because dermatologists often see seborrheic dermatitis in patients who don't have seborrhea, and therefore know that seborrhea is not a subset nor the same as seborrheic dermatitis and seborrheic dermatitis is not a subset of seborrhea. Put another way, a physician will not use a treatment for seborrhea in connection with a disorder, such as seborrheic dermatitis, which is known to be different in both cause and effect from seborrhea.

All statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application and any registration resulting therefrom.

Date: 1/4/06

James Leyden, M.D.

EXHIBIT A

CURRICULUM VITAE

James J. Leyden, M.D.

Personal Data:

Full Name:	*James Joseph Leyden*
Home Address:	*319 Applebrook Drive* *Malvern, PA 19355*
Business Address:	*Skin Study Center* *(KGL, Inc.)* *505 Parkway* *Broomall, PA 19008-4204* *Tel: (610) 544-8848* *Fax: (610) 544-6305*
Date of Birth:	*August 20, 1940*
Place of Birth	*Philadelphia, Pennsylvania*
Citizenship:	*United States of America*
Marital Status	*Married - December 27, 1962* *Wife: Claudette Schilling* *Children: Wendy and James*

Education:

1958-1962	*A.B. Saint Joseph's College*
1962-1966	*M.D. University of Pennsylvania School of Medicine*

Postgraduate Training and Fellowship Appointments:

1966-1967	*Intern Temple University Medical School*
1967-1968	*Resident in Dermatology, University of Pennsylvania*
1967-1968	*United States Public Health Fellow*
1970-1972	*Resident in Dermatology, University of Pennsylvania*

Military Service:

1968-1970	*Chief of Dermatology, U.S. Army, Fort Devens*

Editorial Positions:

1985-1990	*Editorial Board, Journal of the American Academy of Dermatology*
1987-1992	*Editorial Board, Journal of Microbial Ecology in Health and Disease*
1988-1992	*Editorial Board, Medicine Group*
1988-1992	*Editor-in-Chief, Cutaneous Aging and Cosmetic Dermatology*
1993-	*Editorial Advisory Board, Skin & Aging*

Committees:

1993-1997	*American Academy of Dermatology, Board of Directors*
1989-2001	*Dermatology Foundation, Chairman, Board of Trustees*
1987-	*Executive Committee, Dermatology Foundation*
1988-1989	*Vice President, Dermatology Foundation*
	American Academy of Dermatology Infectious Disease Committee Chairman
	American Academy of Dermatology Health Industry Liaison Committee, Chairman
	American Academy of Dermatology Task Force On Steroid Anti-infection Agents, Vice Chairman
	American Academy of Dermatology Government Liaison Committee
	American Academy of Dermatology Therapeutics Committee
	Toxicology Committee, National Academy of Sciences
	Consultant to U.S.A. FDA and FTC
	Consultant to Health Protection Branch
	Canada Consultant to Drug Regulation Agencies of England, Germany, and Austria
1988-2002	*Admissions Committee, School of Medicine, Medical Audit Committee, Hospital of the University of Pennsylvania Utilization Review Committee, Hospital of the University of Pennsylvania*
2003-	*Sub-committee on Acne Management, American Academy of Pediatrics*

Faculty Appointments:

1972-77	*Assistant Professor of Dermatology, University of Pennsylvania School of Medicine*
1972-87	*Chief of Dermatology Clinic, Hospital of the University of Pennsylvania*
1977-83	*Associate Professor of Dermatology, University of Pennsylvania School of Medicine*
1979-	*Affiliated Senior Scientist, Monell Chemical Senses Center*
1983-	*Professor of Dermatology, University of Pennsylvania School of Medicine*
2002	*Professor Emeritus, University of Pennsylvania School of Medicine*
2002	*Adjunct Professor of Dermatology, Northwestern University School of Medicine*

Specialty Certification:

1973 *American Board of Dermatology*

Licensure: *Pennsylvania*

Awards, Honors, and Membership in Honorary Societies:

1962	*Who's Who of American Colleges*
1966	*Alpha Omega Alpha (Honorary Medical Society)*
1971	*Henry W. Stelwagon Award American Academy of Dermatology*
1972	*North American Dermatological Association Award*
1976	*Bronze Award for Original Investigation American Academy of Dermatology*
1985	*Gold Award for Original Investigation American Academy of Dermatology*
1986	*Bronze Award for Original Investigation American Academy of Dermatology*
1986	*Silver Award, Teaching Value American Academy of Dermatology*
1997	*Gold Award for Original Investigation American Academy of Dermatology*
2003	*Honorary Member, Society of Investigative Dermatology*

Memberships in Professional and Scientific Societies:

Society of Investigative Dermatology
American Academy of Dermatology
Infectious Control and Hospital Epidemiology
Philadelphia Dermatologic Society
Philadelphia College of Physicians
American Society of Microbiology
Society of Pediatric Dermatology

Chapters, Reviews & Books

1. *Rudolph,R.I.,and Leyden, J.J.: Immunotherapy in Dermatology Rosenthale, Marvin e., and Herbert C. Mansmann, Jr., (Eds.), Monographs of the Physiological Society of Philadelphia, Vol., 1. Immunopharmacology pp. 315-332, Spectrum Publications, New York, NY, 1975.*

2. *Laskas, J.J., Jr., and Leyden, J.J.: Punctate keratoderma. Arch Derm, 111(7):921, July, 1975.*

3. *Kligman, A.M., McGinley, K.J., and Leyden, J.J.: Kopfschuppen. Ihre Ursachen und Behandlung. In: Har und Haar Krankherten, Herausgegebem von C. Orfanos, Stuttgart und New York: Gustave Fischer Verlag, Seiten 663-680, 1978.*

4. *Leyden, J.J., McGinley, J.J., Mills, O.H., and Kligman, A.M.: Topical Antibiotics and Topical Antimicrobial Agents in Acne Therapy. In: Dermatology Symposium in Lund: Eds. J. Juhlin, H. Rossman, J.S.Strauss. Uppland Giafiska A.B. Uppala, 1980.*

5. *Kligman, A.M., and Leyden, J.J.: The Interaction of Fungi and Bacteria in the Pathogenesis of Athlete's Foot, in: Skin Microbiology: Relevance to Clinical Infection, Howard I. Maibach and Raza Aly (Eds.), published by Springer-Verlag, New York, NY, pp. 203-219, 1981.*

6. *Kligman, A.M., Leyden, J.J., Gross, P., Allen, H., and Rudolph, R.I.: Symposium on Retinoids 245-253, 1981.*

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9. Leyden, J.J., and Kligman, A.M.: Dandruff, in Safety and Efficacy of Topical Drugs and Cosmetics, Albert Kligman and James Leyden (Eds.), published by Grune and Stratton, New York, NY, pp. 182-288, 1982.

10. Leyden, J.J., and Kligman, A.M.: Wound Healing, in Safety and Efficacy of Topical Drugs and Cosmetics, Albert Kligman and James Leyden (Eds.), published by Grune and Stratton, New York, NY, pp. 275-280, 1982.

11. Leyden, J.J. and Kligman, A.M.: Axillary Odor and Deodorant Testing, in Safety and efficacy of Topical Drugs and Cosmetics, Albert Kligman and James Leyden (Eds.), published by Grune and Stratton, New York, NY, pp. 269-274, 1982.

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17. Leyden, J.J.: Follicular Microflora in Acne Vulgaris, W.B. Saunders Company, Philadelphia, PA. Dermatologic Clinics 1.3, pp. 345-351, 1983.

18. Leyden, J.J.: Pathophysiology of Cutaneous Bacterial Infections, Pathophysiology of Dermatologic Diseases. McGraw-Hill Book Company, New York, NY, 1984.

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EXHIBIT B

Volume I

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CHAPTER 124

Gerd Plewig
Thomas Jansen

Seborrheic Dermatitis

Seborrheic dermatitis is a common chronic papulosquamous dermatosis that is usually easily recognized. It affects infants and adults and is often associated with increased sebum production (seborrhea) of the scalp and the sebaceous follicle-rich areas of the face and trunk. The affected skin is pink, edematous, and covered with yellow-brown scales and crusts. The disease varies from mild to severe, including psoriasiform or pityriasiform patterns and erythroderma.[1] Seborrheic dermatitis is one of the most common skin manifestations in patients with human immunodeficiency virus (HIV) infection.[2] Consequently, it is included in the spectrum of premonitory lesions and should be carefully evaluated in high-risk patients.

INCIDENCE

Seborrheic dermatitis has two age peaks, one in infancy within the first 3 months of life and the second around the fourth to the seventh decades of life. No data are available on the exact incidence of seborrheic dermatitis in infants, but the disorder is common. The disease in adults is believed to be more common than psoriasis, for example, affecting at least 3 to 5 percent of the population in the United States.[3] Men are affected more often than women in all age groups. There does not appear to be any racial predilection. Seborrheic dermatitis is found in up to 85 percent of patients with HIV infection.[2]

ETIOLOGY AND PATHOGENESIS

Although many theories abound, the cause of seborrheic dermatitis remains unknown.

Seborrhea

The disease is associated with oily-looking skin (seborrhea oleosa), although an increased sebum production cannot always be detected in these patients.[4] Even if seborrhea does provide a predisposition, seborrheic dermatitis is not a disease of the sebaceous glands. The high incidence of seborrheic dermatitis in newborns parallels the size and activity of the sebaceous glands at this age. It has been shown that newborns have large sebaceous glands with high sebum secretion rates similar to adults.[5] In childhood, sebum production and seborrheic dermatitis are closely connected. In adulthood, however, they are not, as the sebaceous gland activity peaks in early puberty and decades later seborrheic dermatitis may occur.

The sites of predilection—face, ears, scalp, and upper part of the trunk—are particularly rich in sebaceous follicles. Two diseases are prevalent in these regions: seborrheic dermatitis and acne. In patients with seborrheic dermatitis, the sebaceous glands are often particularly large on cross-sectional histologic specimens. In one study, skin surface lipids were not elevated but the lipid composition was characterized by an increased proportion of cholesterol, triglycerides, and paraffin, and a decrease in squalene, free fatty acids, and wax esters.[6] However, mild abnormalities in the skin surface lipids could well result from the ineffective keratinization, which is often demonstrable histopathologically. Seborrheic dermatitis seems to be more frequent in patients with parkinsonism, in whom sebum secretion is increased. Similarly, after reduction of sebum production induced by levodopa and by promestriene, seborrheic dermatitis may improve.

The synonym *eczéma flannelaire* stems from the idea that a retention of skin surface lipids by clothing and rubbing of the rough textiles on the skin—cotton (flannel), wool, or synthetic underwear in particular—promotes or aggravates seborrheic dermatitis.

Microbial Effects

Unna and Sabouraud, who were among the first to describe the disease, favored an etiology involving bacteria, yeasts, or both. This hypothesis has remained unsupported, although bacteria and yeast can be isolated in great quantities from affected skin sites.

In infancy, *Candida albicans* is often found in dermatitic skin lesions and in stool specimens. Although intracutaneous tests with candidin, positive agglutinating antibodies in serum, and positive lymphocyte-transformation tests in affected infants revealed sensitization to *C. albicans*, these observations cannot be convincingly linked to the pathogenesis.

Aerobic bacteria were recovered from the scalp of patients with seborrheic dermatitis (140,000 bacteria/cm^2 versus 280,000 in normal individuals and 250,000 in persons with dandruff). In contrast, *Staphylococcus aureus* was rarely seen in normal persons or those with dandruff. *Staphylococcus* was recovered in about 20 percent of patients with seborrheic dermatitis, accounting for an average of about 32 percent of the total skin flora.[7]

Propionibacterium acnes counts were low in patients with seborrheic dermatitis (7550 bacteria/cm^2 in those without dandruff). The small quantities of *P. acnes* in patients with seborrheic dermatitis may explain the low yield of free fatty acids from their skin surfaces.

The lipophilic yeast *Pityrosporum* is abundant in normal skin (504,000 organisms/cm^2 versus 922,000 in individuals with dandruff and 665,000 in patients with seborrheic dermatitis).[7] This organism has received particular attention in recent years. Some authors claim strong evidence in favor of a pathogenic role for these microbes, whereas others do not share this view. Their argument is that *Pityrosporum ovale* is not the causative organism, but is merely present in large numbers. In patients with pityriasis versicolor[8] and *Pityrosporum* folliculitis,[9] seborrheic dermatitis has been found in a higher percentage than expected. Clearing of seborrheic dermatitis by selenium sulfide and continued suppression of *P. ovale* with topical amphotericin B caused a

relapse of the disease on inflamed scalp skin.[10] In seborrheic dermatitis, both normal and high levels of serum antibodies against *P. ovale* have been demonstrated. A cell-mediated immune response to *P. ovale* has been found in normal individuals using *Pityrosporum* extracts in lymphocyte-transformation studies.[11] Overgrowth of *P. ovale* may lead to inflammation, either through introduction of yeast-derived metabolic products into the epidermis or as a result of the presence of yeast cells on the skin surface. The mechanism of production of inflammation would likely then be through Langerhans cell and T lymphocyte activation by *Pityrosporum* or its by-products. When *P. ovale* comes into contact with serum, it can activate complement via the direct and alternative pathways and this may play some part in the introduction of inflammation.[12] A possible role for this yeast in the pathogenesis of seborrheic dermatitis is supported by the fact that seborrheic dermatitis–like lesions have been shown to be reproducible in animal models by inoculation of *P. ovale*.[13]

Miscellaneous

DRUGS Several drugs have been reported to produce seborrheic dermatitis–like lesions, including arsenic, gold, methyldopa, cimetidine, and neuroleptics.

NEUROTRANSMITTER ABNORMALITIES Seborrheic dermatitis is often associated with a variety of neurologic abnormalities, pointing to a possible influence of the nervous system. These neurologic conditions include postencephalitic parkinsonism, epilepsy, supraorbital injury, facial paralysis, unilateral injury to the ganglion of Gasser, poliomyelitis, syringomyelia, and quadriplegia. Emotional stress seems to aggravate the disease; a high rate of seborrhea is reported among combat troops in times of war.

PHYSICAL FACTORS It has been suggested that cutaneous blood flow and skin temperature may be responsible for the distribution of seborrheic dermatitis.[14] Seasonal variations in temperature and humidity are related to the course of the disease. Low fall and winter temperatures and low humidity in centrally heated rooms are known to worsen the condition. Seborrheic dermatitis of the face was observed in 8 percent of 147 patients receiving PUVA therapy for psoriasis and occurred within a few days to 2 weeks after the beginning of treatment;[15] the patients had no previous history of facial psoriasis or seborrheic dermatitis. Lesions were avoided by masking the face during irradiation.

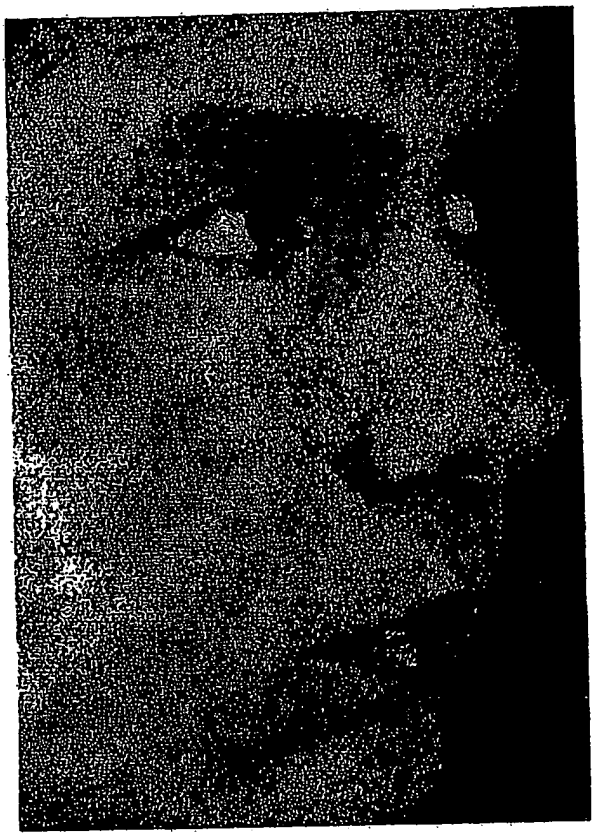
ABERRANT EPIDERMAL PROLIFERATION Epidermal proliferation is increased in seborrheic dermatitis, like psoriasis, explaining why cytostatic therapeutic modalities may improve the condition.[16]

NUTRITIONAL DISORDERS Zinc deficiency in patients with acrodermatitis enteropathica and acrodermatitis enteropathica–like conditions may be accompanied by dermatitis mimicking seborrheic dermatitis of the face. Seborrheic dermatitis is, however, not associated with zinc deficiency nor does it respond to supplementary zinc therapy. Seborrheic dermatitis in infancy may have a different pathogenesis. Biotin deficiency, whether secondary to a holocarboxylase deficiency or a biotinidase deficiency, and abnormal metabolism of essential fatty acids have been proposed as possible mechanisms.[17]

IMMUNODEFICIENCY AND SEBORRHEIC DERMATITIS

The development of seborrheic dermatitis either de novo or as a flare of preexisting disease also may serve as a clue to the presence of HIV infection. The first report of this association in 1984 was followed by observations from all parts of the world.[2] The expression of the disease differs in several aspects from its classical form seen in HIV seronegative individuals (Figs. 124-1 to 124-4): the distribution is extensive, severity is marked, and treatment often difficult (Fig. 124-5). Even the histopathologic changes differ somewhat from those seen in commonly encountered seborrheic dermatitis (Table 124-1).

FIGURE 124-1



Seborrheic dermatitis with involvement of nasolabial folds, cheeks, eyebrows, and nose.

The increased incidence and severity of seborrheic dermatitis in HIV seropositive individuals has led to speculation that unchecked growth of *Pityrosporum* in immunosuppressed patients is responsible. However, a study that compared quantitative *Pityrosporum* cultures in AIDS patients with and without seborrheic dermatitis failed to demonstrate increased yeast colonization in patients with seborrheic dermatitis.[18]

PSORIASIS AND SEBORRHEIC DERMATITIS

In patients with a psoriatic diathesis, particularly adults, seborrheic dermatitis is said to evolve into psoriasis. The term *sebopsoriasis* is sometimes used for these overlapping conditions. It should be used with caution because psoriasis, especially of the scalp, is clinically and histopathologically almost indistinguishable from seborrheic dermatitis.

EXHIBIT C

United States Patent [19]

Pinto et al.

[11] **4,172,149**

[45] **Oct. 23, 1979**

[54] **METHOD FOR TREATING LIVING SKIN EXHIBITING EXCESSIVE SEBUM SECRETION**

[75] Inventors: **Jeffrey S. Pinto, East Aurora, N.Y.; Sung L. Hsia, Miami, Fla.; Paul L. Warner, Jr., Clarence, N.Y.**

[73] Assignee: **Westwood Pharmaceuticals, Inc., Buffalo, N.Y.**

[21] Appl. No.: **873,320**

[22] Filed: **Jan. 30, 1978**

[51] **Int. Cl.²** **A61K 31/23**

[52] **U.S. Cl.** **424/312**; 424/311; 424/313

[58] **Field of Search** 424/311, 312, 314, 313

[56] **References Cited**

U.S. PATENT DOCUMENTS

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Primary Examiner—Leonard Schenkman

Attorney, Agent, or Firm—Morton S. Simon; Irving Holtzman

[57] **ABSTRACT**

Treats living skin in which sebum secretion is excessive with certain triglycerides to reduce the level of sebum secretion.

14 Claims, 4 Drawing Figures

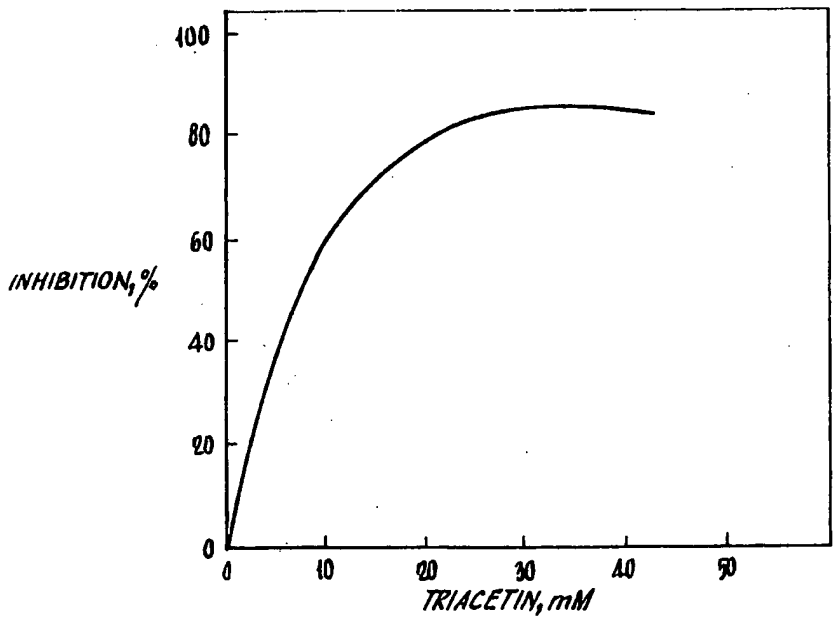

Fig1.

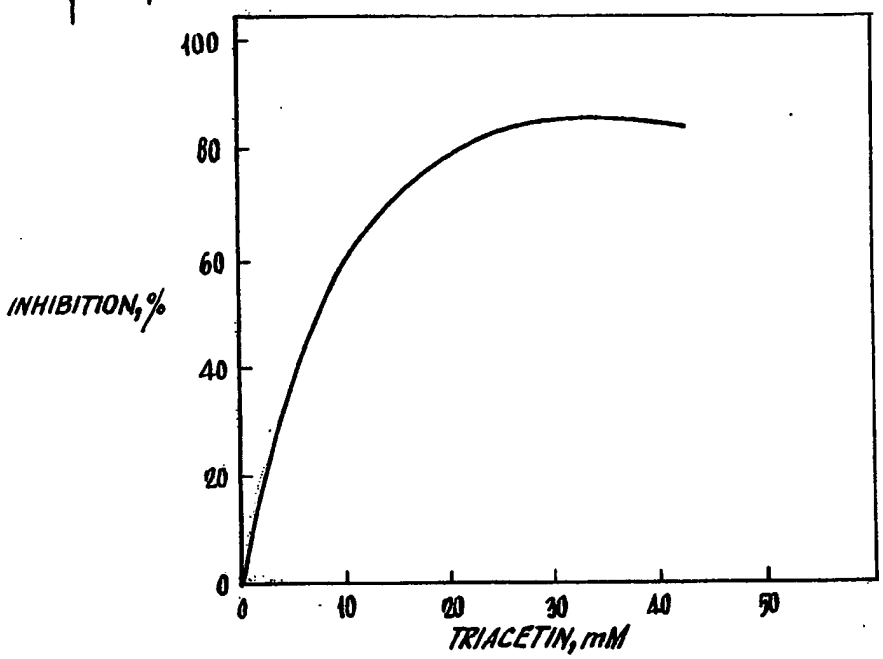
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Fig2.

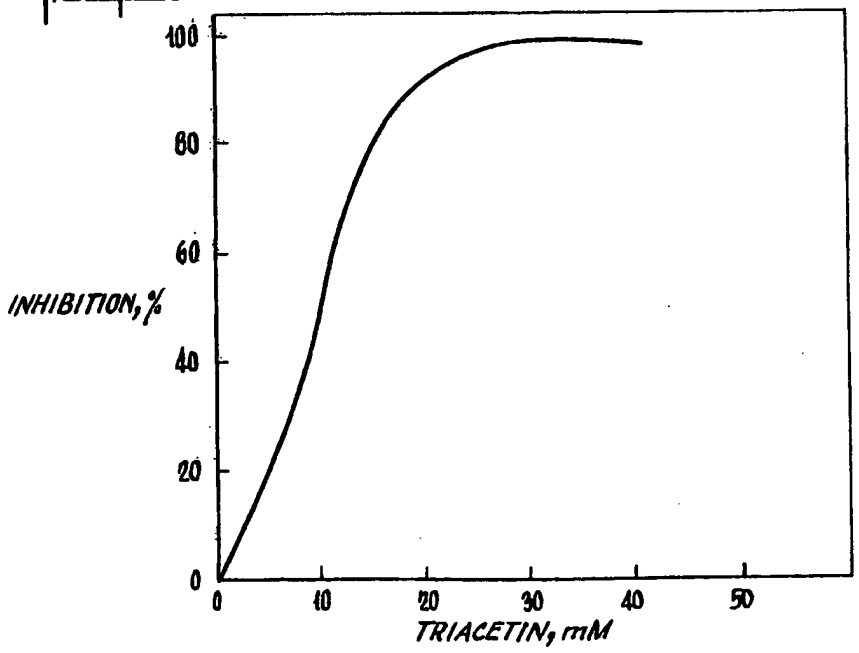
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FIG. 2.

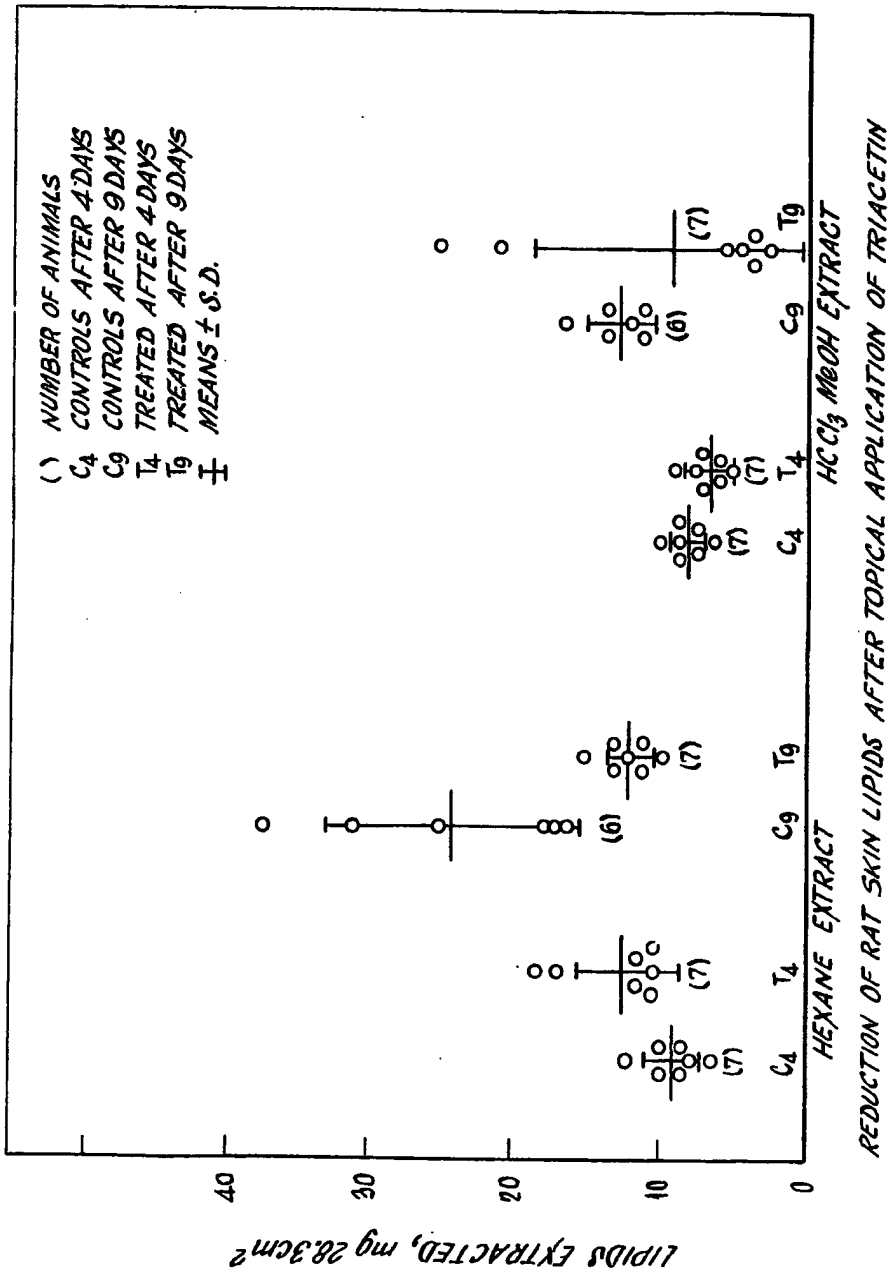
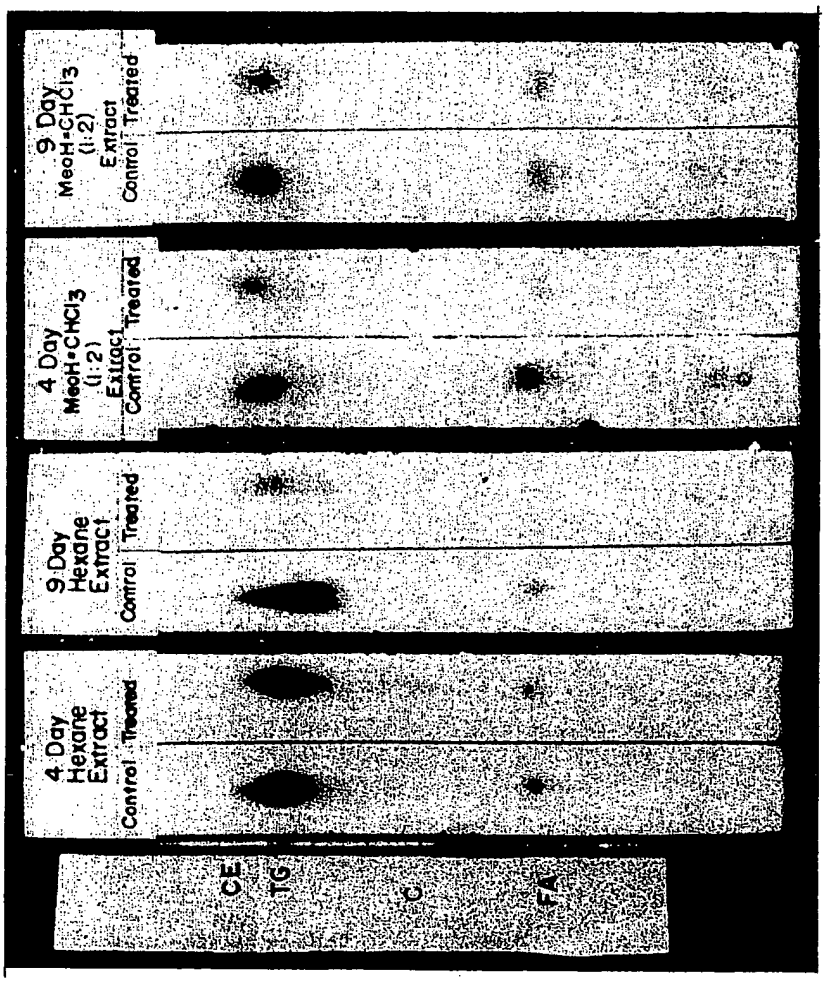

( ) NUMBER OF ANIMALS
C4 CONTROLS AFTER 4 DAYS
C9 CONTROLS AFTER 9 DAYS
T4 TREATED AFTER 4 DAYS
T9 TREATED AFTER 9 DAYS
± MEANS ± S.D.
LIPIDS EXTRACTED, mg 28.3cm²
0
10
20
30
40
C4
T4
C9
T9
(7)
(6)
HEXANE EXTRACT
HCCl3 MeOH EXTRACT
REDUCTION OF RAT SKIN LIPIDS AFTER TOPICAL APPLICATION OF TRIACETIN

Fig. 4.



THIN LAYER CHROMATOGRAPHY OF RAT SKIN LIPIDS

METHOD FOR TREATING LIVING SKIN EXHIBITING EXCESSIVE SEBUM SECRETION

This invention relates to a method for treating living skin in which there is an excessive secretion of sebum. It concerns, for example, the treatment of a group of skin diseases that are associated with seborrhea and generally characterized by an excessive secretion of sebum, which collects on the skin in the form of an oily coating often accompanied by crusts or scales. Moreover, the invention is also applicable to other skin conditions in which the excessive secretion of sebum is only one component of the pathology. The latter case may be exemplified by such skin conditions as acne vulgaris, acne rosacea and seborrheic dermatitis.

Traditionally, attempts have been made to counteract excessive sebum production through frequent washing with soap or detergent scrubs. This, however, has not proven to be very satisfactory. Moreover, it has been suggested that skin greasiness could be reduced by controlling the rate of sebum secretion through diet or hormonal manipulation. This also has met with only very limited success.

In addition, efforts have been made to control the greasiness of skin by the use of topically applied agents. An example of the above is described in U.S. Pat. No. 3,948,943 in which the patentees suggest the use of certain heterocyclic aminocarboxylic acid higher alkylamides for inhibiting sebaceous gland secretion. A further example is described in U.S. Pat. No. 3,984,535 which teaches the use of 2,6-di. tert. butyl paracresol, propyl gallate, butyl hydroxy anisol, octyl gallate or dodecyl gallate in a carrier as a scalp deodorant, and claims that these compositions cause a significant reduction of sebum. Other examples are U.S. Pat. Nos. 4,016,287 and 3,949,087; the former claiming inhibition of sebaceous gland excretion by the topical use of the compound N-(4'-phenyl-benzoyl)-4-amino-butyric acid and the latter, the topical use of d,l-carnitine chloride or l-carnitine chloride, or a mixture of both for the suppression of seborrhea.

It has now been found that sebum production in the living skin can be controlled by controlling the synthesis of the triglycerides, the major components of sebum. More particularly, it has been found that certain fatty acid triglycerides, described in more detail below, are effective blocking agents in the biosynthesis of the sebum triglycerides in the skin. Consequently, they may be employed as topical agents for the management of skin conditions characterized by the over production of sebum.

It is accordingly an object of the present invention to provide a process for reducing the excessive secretion of sebum in living skin.

It is also an object of the present invention to provide a process for treating diseases of the skin in which at least one of the pathoiogical conditions of the disease is an excessive secretion of sebum.

Other and more detailed objects of this invention will be apparent from the following description and claims.

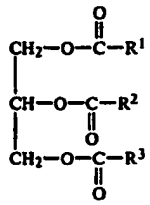
FIG. 1 is a graph summarizing a study showing the percent inhibition of tripalmitin production for excised human skin containing sebaceous glands when incubated with a medium containing [8,9-^{3}H] palmitic acid and triacetin.

FIG. 2 is a graph summarizing a study showing the percent inhibition of tripalmitin production for excised human skin containing sebaceous glands when incubated with a medium containing [U-^{14}C] glucose and triacetin.

FIG. 3 is a graph summarizing a study showing the reduction of rat skin lipids after topical application of triacetin in accordance with the present invention.

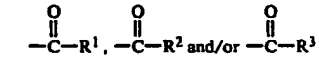
FIG. 4 is a copy of a thin layer chromatograph showing the separation of the fractions contained in extracts from skin that was treated and skin that was untreated with triacetin in accordance with the present invention.

The triglycerides that may be used in accordance with the present invention may be described by the general formula:

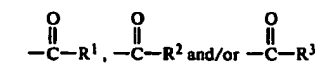


(I)

wherein R^1, R^2 and R^3 are straight chain, branched chain, saturated or unsaturated aliphatic hydrocarbon radicals having from 1 to 20 carbon atoms. R^1, R^2 and R^3 may be the same or a different aliphatic hydrocarbon radical but they most often will be the same radical. In the preferred form of the invention, R^1, R^2 and R^3 represent the same alkyl group and usually a saturated alkyl group having from 1 to 9 carbon atoms. The acyl portion of the triglycerides of Formula I above i.e.



can be derived from a variety of fatty acids. These preferably include such fatty acids having 2 to 10 carbon atoms and particularly acetic acid, n-propionic acid, n-butyric acid, valeric, caproic, enanthylic, caprylic, pelargonic and capric acids. Illustrative of other saturated fatty acids and unsaturated fatty acids that may serve as the source for the acyl radicals



mention may be made of lauric, myristic, palmitic, stearic and arachidic, Δ^9-decylenic, Δ^9-dodecylenic, palmitoleic, oleic, linoleic, linolenic, gadoleic and arachidonic acids. As examples of branched chain triglycerides that may be used in the present invention, mention may be made of isotributanoin, anteisotrioctanoin, isotrihexanoin, anteisotrihexanoin, isotridecanoin, and anteisotridecanoin. In accordance with this invention, single triglycerides or mixtures of triglycerides may be employed for the present purposes. When a mixture of triglycerides is employed, each of R^1, R^2 and R^3 is preferably saturated alkyl having 3 to 9 carbon atoms or a radical containing 7 to 10 carbon atoms. Also preferred are triglycerides wherein R^1, R^2 and R^3 each have from 10 to 20 carbon atoms.

As indicated, the aforesaid triglycerides may be applied to oily living skin i.e. skin in which there is an excessive secretion of sebum to retard the biosynthesis of sebum triglycerides. This process involves coating

the skin area which exhibits an excessive rate of sebum production with a triglyceride product comprising at least about 10% and preferably at least 50% by weight of one or more triglycerides of Formula I up to about 100% by weight of said triglycerides. This is applied in repeated applications over a period of time sufficient and in an amount sufficient to materially reduce the rate of sebum production. These triglycerides may be applied as such in which event they will comprise about 100% by weight of the triglyceride product. They may also be distributed in a pharmaceutically acceptable vehicle. In this case, triglyceride or triglycerides will comprise about at least 10% by weight of the triglyceride product and preferably at least 50%.

For the best results, the triglyceride products of the present invention are applied periodically over a period of time. This will vary with the particular triglyceride or triglycerides that are employed. However, generally an application of the product of at least once a day over a period of about at least 9 or more days will suffice to get the desired results. The treatment will usually continue until the rate of sebum production is reduced to an acceptable level.

The quantity of product to be applied during any one day to get effective results also varies and depends on the particular triglyceride that is selected for use. For example, with tricaprylin, a 34.9% reduction of neutral lipid is seen with doses as low as 0.5 gm/70 cm^2/day for a period of 14 days whereas with tributyrin at a dose of 2 gm/70 cm^2/day for 14 days the reduction is only 10.4%. Other triglycerides tested showed an effective dosage level within this range.

The effectiveness of treatment has been shown to be dose dependent when tricaprylin was applied topically in a range of 0.5–2 gm/70 cm^2/day for 14 days. The reduction in sebum production was 34.9% at 0.5 gm/day, 42.5% at 1 gm/day and 47.3% at 2 gm/day.

The upper limit to the quantity of triglyceride that is to be applied on a daily basis is not critical and depends on factors such as the economics and the elegance of the treatment involved. The blocking effect of the triglycerides appears to increase with the increase in the daily quantity of triglyceride applied. In the upper ranges, as much as 6 gm/day can be employed as an effective lipogenic blocking agent when applied to a living skin area of from about 60 to 75 square centimeters.

The blocking agents described in Formula I above will ordinarily be used in conjunction with a pharmaceutical vehicle. Thus, it will usually be applied in the form of simple solutions, lotions, creams, ointments, etc. A typical composition will contain the active blocking agent in a vehicle in a concentration in the range of from about 10% to 90% by weight based on the total weight of the composition and preferably between about 50% and 90%. Conventional aids ordinarily employed in formulating lotions, creams, ointments and gels such as mineral oil, petrolatum, propylene glycol, stearyl alcohol, sodium lauryl sulfate, carbopol, triethanolamine, water, ethanol, polyethylene glycol may also be incorporated in the composition of the present invention.

The following Examples are given to further illustrate the present invention. It is understood, however, that the invention is not limited thereto.

EXAMPLE 1

Human facial skin was obtained from plastic surgery. Dermis rich in sebaceous glands was prepared after the epidermis was removed with a keratome set at 0.2 mm, and the subcutaneous fat was trimmed off with a pair of scissors. The preparation was cut into squares of 1 cm^2. Each square was incubated at 37° C. for 2 hours with either 5μ Ci of [8,9-^{3}H] palmitic acid (0.2 mM) or 5μ Ci of [U-^{14}C] glucose in a medium consisting of 1 ml Krebs-Ringer bicarbonate buffer containing 5.5 mM glucose, 4% bovine serum albumin, gassed to pH 7.4 under O_2:CO_2 (95:5) with or without triacetin (4.5 to 41 mM). At the end of the incubation, the tissue was removed from the incubation medium, rinsed three times with saline and homogenized in 3 ml of chloroform methanol (2:1). The lipid extract was subjected to TLC developed sequentially in ethyl ether:benzene:acetic acid: ethanol (40:50:0.2:2) and ethyl ether-hexane (6:94). Radioactivity in the triglyceride fraction was assayed by scintillation counting. Inhibition of triglyceride synthesis was expressed as a percentage of the control value (without inhibitor). The results are shown in FIGS. 1 and 2.

In FIG. 1 the results are summarized for the experiments in which [8,9-^{3}H] palmitic acid was contained in the incubation medium. The percent inhibition of tripalmitin production is plotted against the concentration of triacetin contained in the incubation medium. This demonstrates the inhibition on the formation of tripalmitin from [8,9-^{3}H] palmitic acid by triacetin. The results are obtained by comparing the level of tripalmitin obtained in the control incubation experiments (no triacetin) with that obtained in the experiments that employ various concentrations of triacetin in the incubation medium (4.5 to 40 mM).

In FIG. 2 the results are summarized for the experiments in which [U-^{14}C] glucose is contained in the incubation medium. Here again, the percent inhibition of tripalmitin production is plotted against the concentration of triacetin in the incubation medium. In this case, however, the effect of triacetin was calculated on the basis of the ^{14}C incorporated in the triglyceride fraction. FIG. 2 demonstrates the inhibition on the formation of tripalmitin from [U-^{14}C] glucose by triacetin. As in the case with FIG. 1, the results are obtained by comparing the level of tripalmitin obtained in the control experiment (no triacetin) with that obtained in the experiments that use various concentrations of triacetin (4.5 to 40 mM).

It is to be noted that in each case a dose response curve is obtained. That is to say, that the percent inhibition of tripalmitin production increases with a corresponding increase in the concentration of the triacetin in the incubation medium.

EXAMPLE 2

Male Spraque-Dawley rats weighing 250–350 g were fed Purina Rat Chow ad lib and kept in individual cages. On day 0, the hair on the back of the animals was clipped with a hair clipper, and the back was washed with hexane. The animals were then divided into two groups. Group A were controls and were not treated with any topical agent. Group B were treated topically, once each day, with glyceryl triacetate (triacetin). The amount of triacetin applied was 400 μl to an area of approximately 77 cm^2 on the back where the hair had been clipped. On day 4 and day 9, six or seven animals from each group were killed by asphyxiation in CO_2. The skin on the back was immediately removed and mounted on a lipid extractor.

The skin lipids were first extracted with 10 ml of hexane six times. The extracts were pooled and filtered to remove the dirt and tissue debris, and evaporated to dryness in a tared aluminum planchet. The weight of the residue was determined on an analytical balance. The hexane extract contains mostly triglycerides.

The skin was then extracted six times with 10 ml of $HCCl_3$:MeOH (2:1) and the weight of the residue from this extract was also determined gravimetrically. In previous experiments, it was found that six extractions with these solvents exhaustively removed the lipids on the skin under the stated conditions.

For further analysis of the lipids extracted from rat skin, aliquots of the lipid residues were applied to thin layer plates of Silica Gel G, which were developed in the solvent system of benzene:ethyl acetate:ether:acetic acid (80:10:10:0.2, v/v) according to Storry and Tuckley (Lipids 2:501, 1967). The lipids were visualized by a spray of phosphomolybdic acid.

FIG. 3 shows the weights of lipids extracted from the skin of control rats and rats treated topically with triacetin. It is seen that after 4 days of treatment, there was no significant difference between the weights of the lipids extracted from the surface of the skin of the two groups of animals. Clear differences were, however, observed after 9 days of treatment. The reduction in skin surface lipids of the treated animals was about 50%. The amount of lipids from the treated animals practically remained the same on day 9 as on day 4, while from day 4 to day 9 the lipids from the controls more than doubled. A 5 μl aliquot of the residue from the hexane extract (dissolved in 1 ml of hexane), and a 10 μl aliquot of the residue from the $HCCl_3$:MeOH (2:1) extract (dissolved in 1 ml of $HCCl_3$:MeOH) were applied to thin layer plates.

FIG. 4 shows that after 9 days of treatment, the triglyceride fraction (TG) in the hexane extract was drastically reduced, and the free fatty acid fraction (FA) virtually disappeared. A reduction in TG and FA was also observable in the $HCCl_3$:MeOH extract after 4 days of treatment.

These results indicate that topical application of triacetin effectively reduces skin surface lipids in the rat. The effect was not obvious after 4 days of treatment, but became clear after 9 days. Analysis by thin layer chromatography indicated that the reduction was mainly in TG and FA fractions of the skin of the treated animals.

EXAMPLE 3

Adult male Sprague-Dawley rats weighing 240–280 g were fed Purina Chow ad lib and kept in individual cages. On day 1, the hair on the back of the animals was clipped with a hair clipper and the back was washed with hexane. The animals were then divided into control and experimental groups.

Topical Treatment with Test Compounds

The control group was not treated with any topical agent. The experimental groups were treated topically with tributyrin, tricaproin and tricaprylin each day for 14 days. The triglycerides were directly pipetted onto an area of approximately 60 to 75 cm^2 on the back where the hair had been clipped. The application was once daily.

Extraction of Lipids

On day 14, the animals were killed by asphyxiation in CO_2. The skin in the back was immediately removed and mounted on the lipid extractor. The area of skin extracted was 28.3 cm^2. The accumulated lipids on the surface were first extracted six times with 10 ml hexane to remove neutral lipids. The skin was then extracted six times with 10 ml of $CHCl_3$:CH_3OH (2:1) to remove polar lipids. The neutral lipid and polar lipid extracts were pooled separately and filtered through glasswool and filter paper to remove dirt and tissue debris. The solvent was removed by evaporation and the residues were dried at 100° C. overnight. The weight of the residue was determined on an analytical balance.

Hydrolysis of Neutral Lipids

The lipid residue from the hexane extract was hydrolyzed with 3 ml of 1 N KOH in methanol at 100° C. At the end of 2 hours, the hydrolysate was acidified with 6 N HCl. The lipids were extracted three times with 6 ml dichloromethane and the pooled extracts were washed three times with water. The solvent was then removed under a jet of N_2 and the residue dried at 100° C. overnight. The weight of the residue was determined on an analytical balance.

In control experiments after hydrolysis and acidification, 30 mg of tricaprylin yielded a residue of 0.5 mg, while 20.6 mg of tripalmitin yielded a residue of 19.1 mg.

The Appearance of Skin and Hair

Rats treated with tricaproin and tricaprylin up to 2 g daily, displayed no visible abnormality of skin or hair growth.

Reduction of Neutral Lipids

The neutral lipids from both control animals and animals treated with the triglycerides were subjected to alkaline hydrolysis. The results are shown in Table I. C4, C6 and C8, respectively, refer to tributyrin, tricaproin and tricaprylin, respectively.

TABLE I

	Neutral Lipids*	% Decrease
Control	15.74±2.48(5)	
C4 2 g/d	15.0±3.6(2)	10.4
C6 1 g/d	12.0±2.7(3)	23.8
2 g/d	10.6±1.7(2)	32.7
C8 .5 g/d	10.25±1.5 (4)	34.9
1 g/d	9.05±1.0(6)	42.5
2 g/d	8.30±1.3(4)	47.3

*The Values are weights in mg per 28.3 cm^2 of skin. Values of neutral lipids were obtained after removal of contaminating C_4, C_6 or C_8 by hydrolysis. The hydrolysates were acidified and extracted with dichloromethane.

These results indicate that tributyrin (C_4) is slightly effective at a 2 g/day level in reducing the neutral lipids in rat skin after a period of treatment of two weeks. Tricaproin (C_6) and tricaprylin (C_8) on the other hand were effective even at a level as low as 1 g/day and 0.5 g/day respectively.

EXAMPLE 4

When applied topically to rats, trioctanoin reduced the skin surface lipids. This is demonstrated in the following experiment.

Adult Male Sprague-Dawley rats weighing 280–320 g were fed Purina Chow ad lib and kept in individual cages. The hair on the back was clipped with a hair

clipper and the back was washed with hexane. The experimental animals were then treated with 0.5, 1 or 2 g of trioctanoin by applying the oil once daily for two weeks to approximately 60–75 cm^2 of the back where the hair had been clipped. The animals were killed and the skin removed and mounted on a special skin lipid extractor. The area extracted was 28.3 cm^2. The accumulated neutral lipids on the skin surface were extracted six times with 10 ml hexane. The residual trioctanoin was removed by hydrolysis in 1 N KOH. After acidification and extraction with dichloromethane, the solvent was evaporated under a stream of N_2. The weight of residue in mg is presented in the Table II below. The number in parenthesis indicates number of animals. In control experiments, after the hydrolysis of 30.0 mg trioctanoin, the weight of octanoic acid in the dichloromethane extract was 0.5 mg.

TABLE II

Rats	Neutral Lipids in Skin Surface	% of Decrease
Control	17.45±0.2(2)	
Treated		
0.5 g/day	10.25±1.5(4)	41.3
1 g/day	6.9±0.8(3)	60.5
2 g/day	6.4±0.9(2)	63.4

EXAMPLE 5

In preliminary clinical tests, the patients were instructed to clean their skin thoroughly with soap and water and then apply 1 gm of tricaprylin to the face 2X/day. In one teenage girl, pimples on the face underwent marked regression in 2–3 days. Another teenage girl showed marked improvement over the same time interval and rated the treatment as very effective and equal to the marketed product, Retin A (retinoic acid). In one male teenager, the improvement in his facial acne after 2 weeks was gauged excellent; in this individual, the response to tricaprylin was considered by the subject and his parents to be much better than that seen previously to Retin A. In a further teenage boy applying the same regimen of tricaprylin to one side of his face and Retin A to the other side according to the directions specified on the package, the tricaprylin side improved more rapidly and to a greater extent. A middle aged woman with mild seborrhea, acne, and very sensitive skin found that tricaprylin applied as above greatly improved her condition and was nonirritating.

The triglycerides of the present invention may be employed in a variety of dosage forms. Thus, they may be made up into gels, solutions, lotions or creams. Typical dosage forms of these types are given below.

GELS

Ingredient	% by Weight														
	Ex. 6	Ex. 7	Ex. 8	Ex. 9	Ex. 10	Ex. 11	Ex. 12	Ex. 13	Ex. 14	Ex. 15	Ex. 16	Ex. 17	Ex. 18	Ex. 19	Ex. 20
Triacetin	50	50	—	—	—	—	—	—	—	—	50	—	—	—	—
Tributyrin	—	—	50	50	—	—	—	—	—	—	—	50	—	—	—
Tricaproin	—	—	—	—	50	50	—	—	—	—	—	—	50	—	—
Tricaprylin	—	—	—	—	—	—	50	50	—	—	—	—	—	50	—
Trioctanoin	—	—	—	—	—	—	—	—	50	50	—	—	—	—	50
Mineral Oil	38	40	38	40	38	40	38	40	38	40	38	40	38	40	38
Cabosil	12	10	12	10	12	10	12	10	12	10	—	—	—	—	—
Microthene (Polyethylene)	—	—	—	—	—	—	—	—	—	—	12	10	12	10	12

SOLUTIONS

Ingredient	% by Weight						
	Ex. 21	Ex. 22	Ex. 23	Ex. 24	Ex. 25	Ex. 26	Ex. 27
Triacetin	10	50	—	—	—	—	—
Tributyrin	—	—	50	10	—	—	—
Tricaproin	—	—	—	—	10	—	—
Tricaprylin	—	—	—	—	—	50	—
Trioctanoin	—	—	—	—	—	—	10
Ethyl Alcohol	QS 100%	QS 100%	QS 100%	QS 100%	QS 100%	QS 100%	QS 100%

LOTIONS

Ingredient	% by Weight					
	Ex. 28	Ex. 29	Ex. 30	Ex. 31	Ex. 32	Ex. 33
Tributyrin	50	—	—	50	—	—
Tricaproin	—	50	—	—	—	50
Tricaprylin	—	—	50	—	50	—
Arlacel 186	4	—	—	—	—	—
Arlacel 83	—	10	—	—	—	—
Preservative	QS	QS	QS	QS	QS	QS
Tween 60	—	—	3	—	3	10
Atmol 84	—	—	—	10	—	—
Water	46	40	47	40	47	40

CREAMS

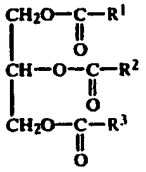
Ingredient	% by Weight					
	Ex. 34	Ex. 35	Ex. 36	Ex. 37	Ex. 38	Ex. 39
Tributyrin	50	—	—	50	—	—
Tricaproin	—	50	—	—	50	—
Tricaprylin	—	—	50	—	—	50
Arlacel 83	5	10	5	—	—	—
Beeswax	2	—	2	2	—	5
Ceresin	—	5	—	—	2	—
Arlacel 60	—	—	—	5	—	5
Tween 60	—	—	—	—	10	—
Preservative	QS	QS	QS	QS	QS	QS

-continued

	CREAMS % by Weight					
Ingredient	Ex. 34	Ex. 35	Ex. 36	Ex. 37	Ex. 38	Ex. 39
Water	43	35	43	43	38	40

What is claimed is:

1. A method for treating an area of living skin from which sebum is secreted at an excessive rate to reduce the rate of sebum production from said area of skin which comprises coating said skin area with a triglyceride product comprising at least about 10% by weight and up to about 100% by weight of a triglyceride or a mixture of triglycerides for a time sufficient and in a therapeutically sufficient amount to reduce the rate of sebum production; said triglyceride or triglycerides being of the formula:



in which R^1, R^2 and R^3 are the same and are straight chain or branched chain saturated or unsaturated aliphatic hydrocarbon radicals containing 1 to 20 carbon atoms.

2. The method according to claim 1 in which said triglyceride product is applied at least once a day for a period of at least nine days.

3. The method according to claim 1 in which the triglyceride or triglycerides employed are such that R^1, R^2 and R^3 are saturated alkyl radicals having 1 to 9 carbon atoms.

4. The method according to claim 1 in which the triglyceride or triglycerides employed are such that R^1, R^2 and R^3 in said formula each have from 10 to 20 carbon atoms.

5. The method according to claim 1 in which the triglyceride product employed contains a mixture of triglycerides in which R^1, R^2 and R^3 in said formula are each radicals containing 7 to 10 carbon atoms.

6. The method according to claim 1 in which the triglyceride or triglycerides employed are such that R^1, R^2 and R^3 in said formula are each branched chain aliphatic hydrocarbon radicals.

7. The method according to claim 1 in which the triglyceride or triglycerides employed are such that R^1, R^2 and R^3 in said formula are each saturated alkyl radicals having 3 to 9 carbon atoms.

8. The method according to claim 1 in which the triglyceride or triglycerides are applied at the daily dosage levels of at least about 0.5 gms/day of triglyceride or triglycerides.

9. The method according to claim 8 in which the triglyceride is triacetin.

10. The method according to claim 8 in which the triglyceride is tributyrin.

11. The method according to claim 8 in which the triglyceride is tricaprylin.

12. The method according to claim 8 in which the triglyceride is tricaproin.

13. The method according to claim 1, wherein said excess rate of sebum secretion in said skin area is associated with acne.

14. The method according to claim 1, wherein said excess rate of sebum secretion in said skin area is associated with seborrhea.

* * * * *

EXHIBIT D

US006120756A

United States Patent [19]

Markowitz

[11] Patent Number: 6,120,756

[45] Date of Patent: Sep. 19, 2000

[54] TOPICAL ANIONIC SALICYLATE FOR DISORDERS OF THE SKIN

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[73] Assignee: **Philip I. Markowitz**, Philadelphia, Pa.

[21] Appl. No.: **09/136,267**

[22] Filed: **Aug. 19, 1998**

[51] **Int. Cl.**[7] **A61K 7/06**; A61K 7/00; A61K 7/42; A61K 6/00

[52] **U.S. Cl.** **424/70.1**; 424/70.11; 424/401; 424/59; 514/887; 514/844; 514/845; 514/846; 514/847

[58] **Field of Search** 424/70.1, 70.11, 424/401, 59; 514/887, 844, 845, 846, 847

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Primary Examiner—Johann Richter
Assistant Examiner—Diedra Faulkner

[57] **ABSTRACT**

A method of treating or preventing a skin disorder caused by at least one of excessive sebum production and abnormal keratinocyte proliferation, the method comprising topically administering to a region of the skin of a human affected by or susceptible to a skin disorder caused by at least one of excessive sebum and abnormal keratinocyte proliferation, a composition comprising anionic salicylate in an amount effective to reduce or stop the occurrence or delay the occurrence of at least one of the excessive sebum production and abnormal keratinocyte proliferation.

19 Claims, 5 Drawing Sheets

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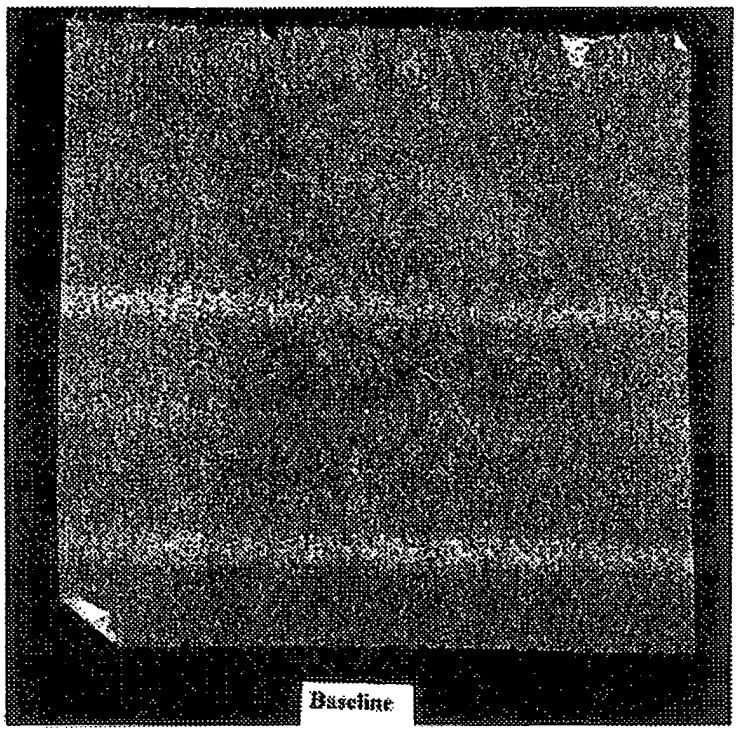

FIG. 1

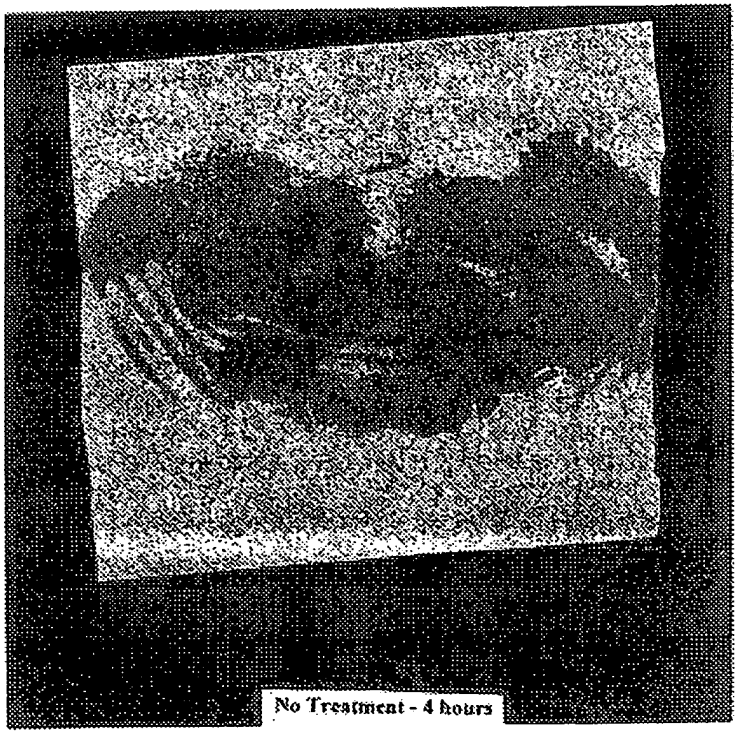

FIG. 2

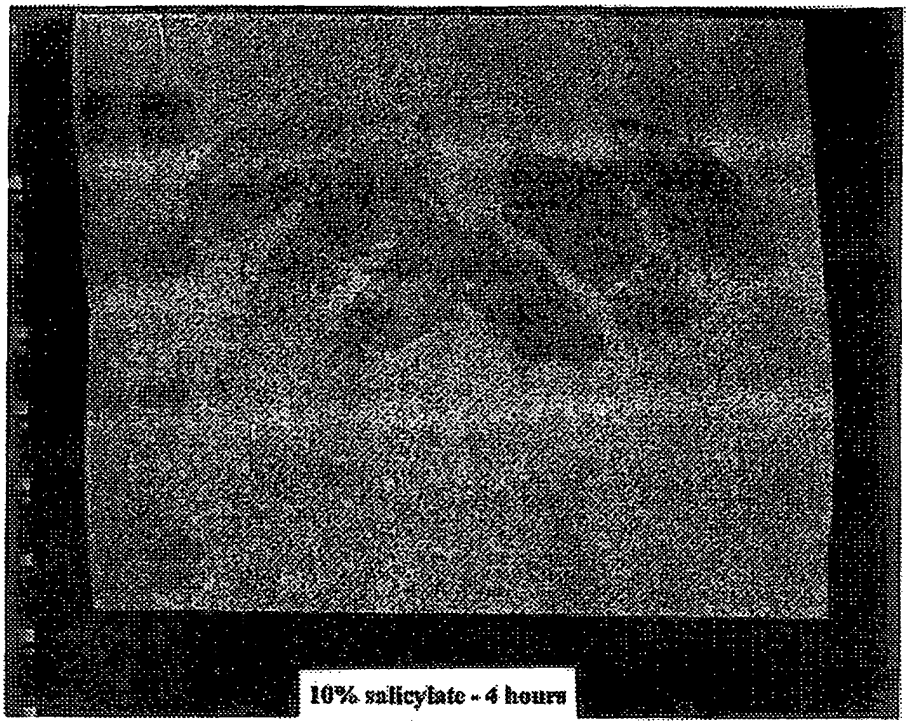

FIG. 3

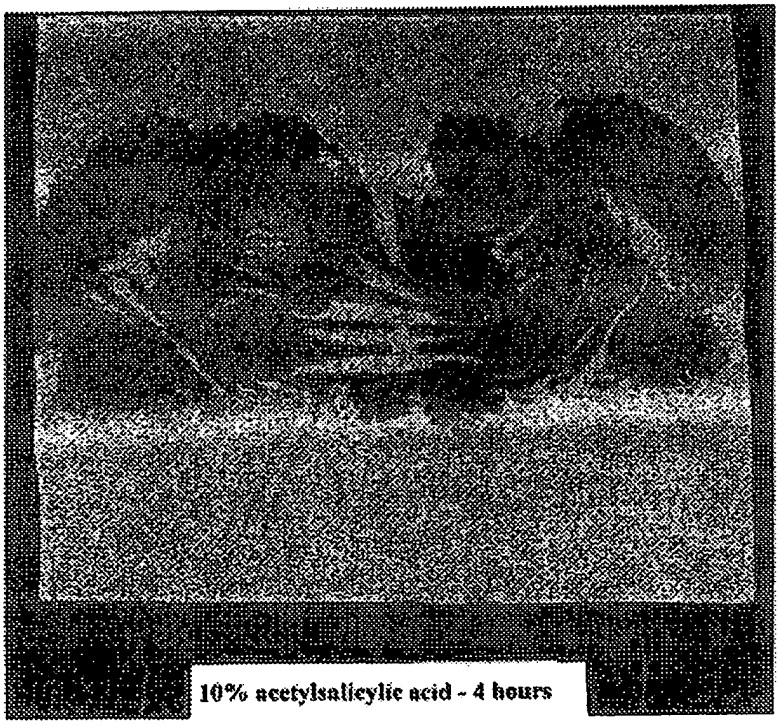

FIG. 4

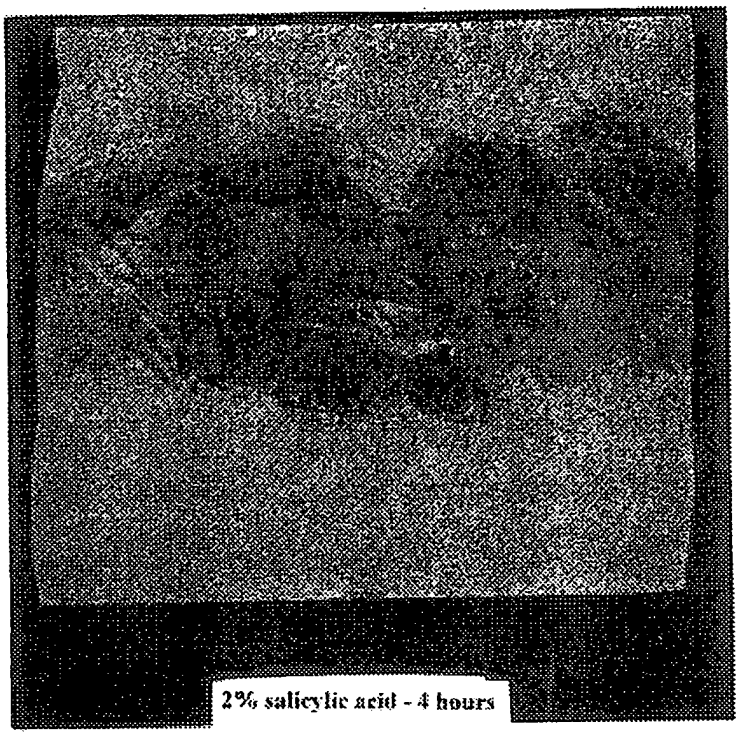

FIG. 5

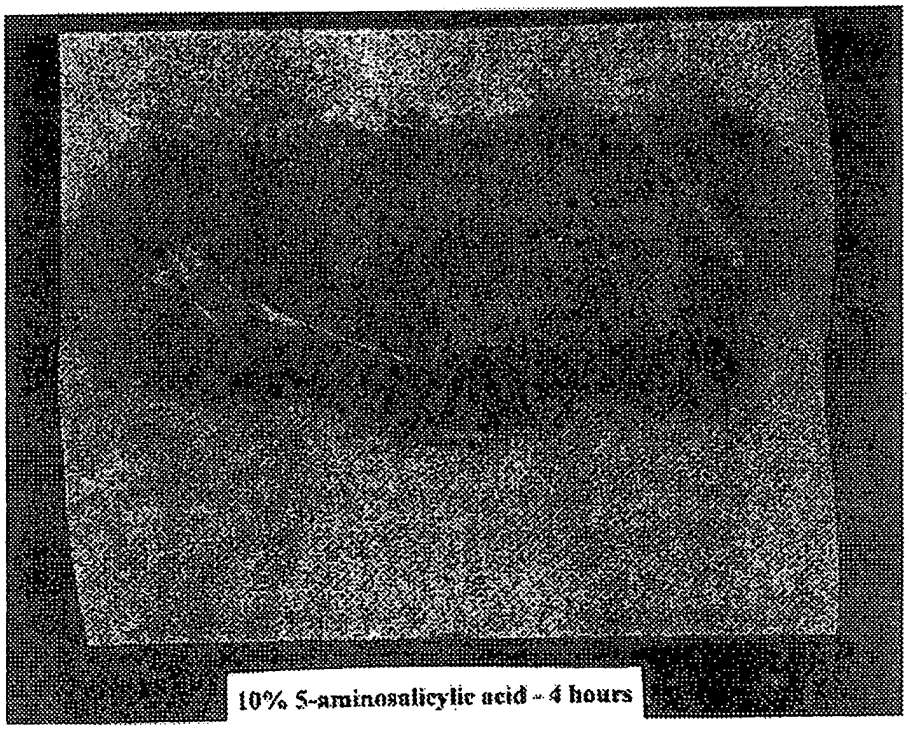

FIG. 6

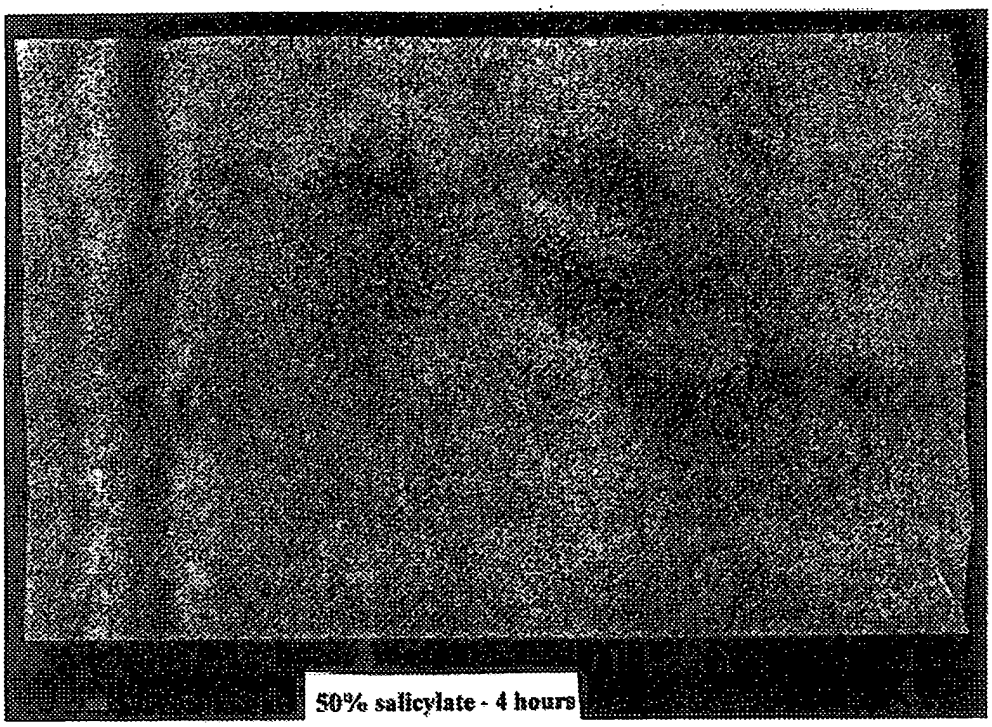

FIG. 7

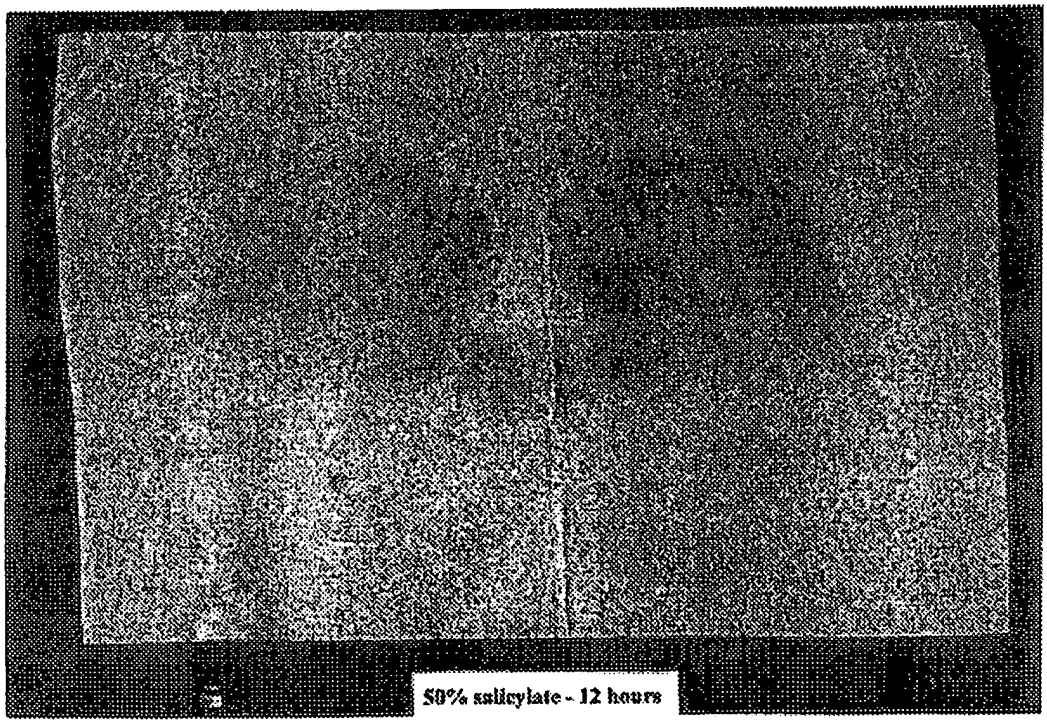

FIG. 8

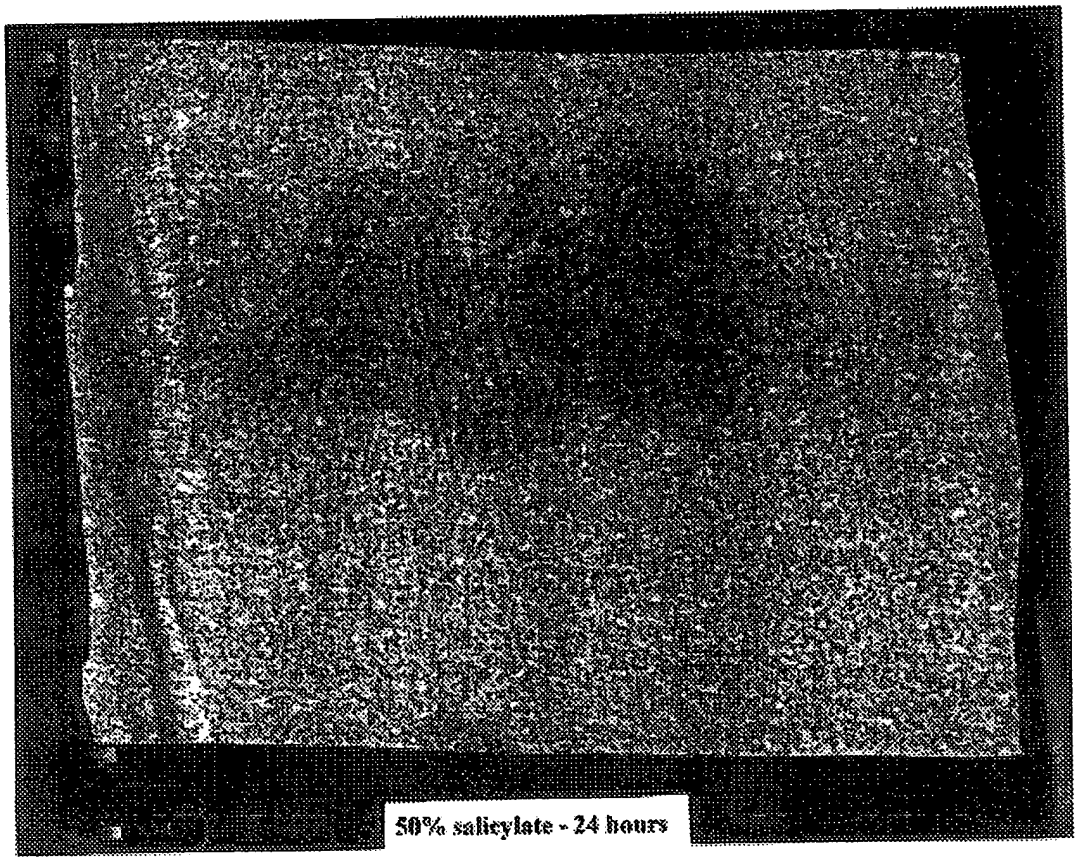

FIG. 9

TOPICAL ANIONIC SALICYLATE FOR DISORDERS OF THE SKIN

FIELD OF THE INVENTION

The present invention relates to treatment and prevention of skin disorders caused by excessive production of sebum, or abnormal proliferation of keratinocytes, or both.

BACKGROUND OF THE INVENTION

There are many skin disorders associated with the excessive production of sebum, or the abnormal proliferation of keratinocytes, or both. Examples of skin disorders include acne vulgaris, seborrheic dermatitis (also referred to as seborrheic eczema), seborrheic adiposa (also referred to as seborrheic oleosa), seborrheic sicca, psoriasis, eczema, contact dermatitis, irritant dermatitis, ichthyosis and keratosis pilaris. Seborrheic dermatitis is characterized by moderate erythema, dry, moist, or greasy scaling, and yellow crusted patches on various skin areas of the body, including the mid-parts of the face, ears, supraorbital regions, umbilicus, genitalia, and especially the scalp. Seborrheic adiposa is described as oily secretion occurring especially about the nose and forehead. Seborrheic sicca is characterized as dry scaly seborrheic dermatitis. Psoriasis is characterized by scaly, erythematous plaques that may become confluent. Ichthyosis is a non-inflammatory scaling, hyperkeratotic disorder of skin. Keratosis pilaris, or multiple keratin plugs in skin follicles, produces a bumpy appearance to the skin. Hyperkeratosis is common in chronic contact, irritant and atopic (eczema) dermatitis.

Acne vulgaris, more commonly called acne, is a common skin disorder affecting a large number of people. Acne can result in physical damage such as scarring or disfigurement. Additionally, acne can cause adverse emotional effects to the individuals afflicted with the condition. Acne results when sebaceous follicles, located primarily on the face and trunk, become obstructed with sebum and epithelial cells. Sebum is produced by sebaceous glands in the follicles and epithelial cells are desquamated from the walls of the follicles. The sebum and the desquamated epithelial cells obstruct the sebaceous follicles. Obstruction of the follicles creates microcomedones which may evolve into comedones (non-inflammatory lesions, e.g., open and closed comedones, i.e., whiteheads and blackheads) or inflammatory lesions (e.g., inflammatory nodules, pustules and papules). A residing anaerobic bacterium, *Propionibacterium acnes* (*P. acnes*) proliferates in this environment of excessive sebum and follicular cells and may produce localized inflammation. Acne can be primary (idiopathic) or secondary (due, for example, to the application of cosmetics). Included in the definition of acne for the purposes of the present invention are cosmetically undesirable skin conditions commonly referred to as pimples, blemishes, skin imperfections, etc.

Acne is currently treated either topically or systemically (Leyden, 1997, *New Engl. J. Med.* 336(16):1156–1162). Treatment of acne involves controlling sebum production, reducing epithelial cell proliferation, or both. The primary etiologic factor in acne is now thought to be excessive sebum production. A treatment best able to modify this will be most efficacious. The present state of the art is such that treatment with systemic drugs is the only current way to control excessive sebum production. These drugs are prescribed as therapies only in severe cases of acne. Drugs known to be effective in controlling sebum overproduction include estrogens, antiandrogens such as cyproterone acetate, spironolactone, and the retinoid isotretinoin.

Estrogen treatments for reducing sebum production are usually prescribed as a combination estrogen-progestin contraceptive. A high dose of estrogen is maximally beneficial, increasing the well-known risks of oral contraceptive therapy. A therapeutic response is slow in onset, not appearing for two to four months. Prolonged treatment is necessary. There are also disadvantages to the use of spironolactone to reduce sebum production. Maximal benefits of spironolactone are also delayed, and continual treatment with the drug is necessary to maintain the improvement. Therapeutic results are only modest because spironolactone is only a weak anti-androgen.

Because sebaceous glands are androgen-dependent, systemic administration of anti-androgens, such as cyproterone acetate, is an effective treatment. However, the use of anti-androgens is limited to nonpregnant women because of potential feminizing effects on a male fetus and demasculinizing effects in adult males.

In severe recalcitrant cases of acne, oral administration of isotretinoin is effective in reducing sebum production, but the use of this compound is limited by cost, adverse side effects and teratogenicity.

Antibiotics, both systemic and topical, are used to decrease the proliferation of *P. acnes*, the bacterium responsible for the inflammatory lesions of acne. Systemic antibiotic treatments include tetracycline, erythromycin, minocycline, doxycycline, clindamycin, and trimethoprim-sulfamethoxazole. Topical antibiotic therapy for acne may include the administration of erythromycin, clindamycin, sulfacetamide, azelaic acid, benzoyl peroxide, or a combination of benzoyl peroxide and either erythromycin or glycolic acid. Although *P. acnes* is sensitive to many antibiotics in vitro, delivery of the antibiotics to the lipid-rich environment of the sebaceous follicles, in which the organism resides and proliferates, is difficult. Erythromycin is poorly lipophilic, clindamycin somewhat more so. Their efficacy is comparable. Benzoyl peroxide, although more lipophilic, also has its limitations. Although benzoyl peroxide is more effective in suppressing the growth of *P. acnes* than the topical formulations of clindamycin and erythromycin, benzoyl peroxide does not have any antinflammatory properties. Moreover, another disadvantage to using benzoyl peroxide in acne treatment is the local irritation and allergic contact dermatitis that may occur in the area of the skin being treated. Animal studies suggest that it may be carcinogenic. The disadvantage of using antibiotics as a treatment of acne is that most individuals require prolonged or frequent intermittent courses of antibiotic administration. Additionally, *P. acnes* is beginning to develop some antibiotic resistance, calling into question the future efficacy of antimicrobial therapy. It also contributes to the generalized development of antibiotic resistance in other pathogenic bacteria. Serious drug reactions have been associated with the use of clindamycin and sulfa drugs.

There has been little therapeutic progress since the introduction of retinoic acid and benzoyl peroxide two decades ago. Azelaic acid, just recently introduced, is not superior to any other topical therapies. Oral isotretinoin is highly effective but not widely available or applicable due to its significantly adverse side effect profile. The strict requirement for contraception is difficult to enforce, particularly in adolescents. There is clearly a need for an effective, safe and cosmetically palatable topical acne treatment.

The prior art describes no topical therapy for decreasing sebum production. Currently, excessive production of sebum is typically treated with facial cleansers, like soaps,

detergents, and astringents, that work by merely removing sebum from the surface of the skin, rather than by reducing or inhibiting sebum production. The use of facial cleaners is actually counterproductive for a number of reasons. Cleansers and astringents emulsify necessary epidermal lipids and overly dry the skin. They paradoxically increase sebum production by causing hyperplasia of sebaceous glands and an increase in the cellular organelles responsible for sebum synthesis in sebocytes. Facial oiliness can be masked by "oil free" cosmetic preparations that contain clays, talcs, silicas, starches, polymers and other materials that temporarily absorb oil like a sponge. These formulations are limited by their sebum-absorbing capacity, formulation difficulties, negative aesthetic properties, and limited duration of effect. Women with acne may attempt to camouflage the symptoms by excessive application of makeup. Makeup is comedogenic and produces additional acne lesions.

Excessive follicular epithelial proliferation, keratinization and desquamation in sebaceous follicles leads to the formation of microcomedones. Known topical therapies for modifying the desquamation of follicular epithelial cells include the administration of retinoids such as tretinoin, isotretinoin and tazarotene, and the desquamating agent salicylic acid. Abnormal proliferation of keratinocytes produces follicular plugging, allowing sebum stasis and bacterial overgrowth. This results in increased bacterial hydrolysis of triglycerides to irritating free fatty acids and the inflammatory papulopustular lesions characteristic of acne.

Salicylic acid, therapeutically classified as a keratolytic agent, is extensively used as a desquamating agent. Salicylic acid exfoliates skin and leads to the extrusion of comedones, the primary lesion of acne. Unfortunately, salicylic acid is irritating and is limited to concentrations that are only partially efficacious. Salicylic acid has no effect on the production of sebum. Salicylic acid is not the preferred topical treatment; rather, benzoyl peroxide is more commonly used, suggesting that salicylic acid has only modest efficacy in the treatment of acne. In acne preparations, salicylic acid is used in concentrations of 0.5% to 2.0%. At a concentration of 0.5%, this compound is probably ineffective, at best minimally effective; however, the 0.5% concentration is marketed for the treatment of acne in individuals with sensitive skin. Salicylic acid at a concentration of 2.0% has modest efficacy. Efficacy potentially could be enhanced by increasing the concentration, however, such increased concentrations are contraindicated, since salicylic acid is extremely irritating because of its high acidity with a pH of 2.4. At a concentration of 17%, salicylic acid is commercially available to treat verruca vulgaris (warts) but carries a warning that this compound should not be applied to normal skin surrounding the lesion; irritated, infected or reddened skin; moles, birthmarks or hairy warts; or the face or mucuos membranes. Diabetics or individuals with circulatory problems are advised not to use it due to the risk of severe ulceration (*Physicians' Desk Reference,* Medical Economics Company, Montvale, N.J., p. 982 (1998). Salicyclic acid at a concentration of 5% is marketed to peel callouses and excessively cornified skin. It would not be appropriate for the tender and less cornified skin of the face. The prior art discloses methods to decrease its irritant properties by combination with pantothenic acid (U.S. Pat. No. 5,612,324) and ascorbic acid (U.S. Pat. No. 5,516,793). Its use in acne is reserved for mild cases primarily involving comedones and papules without a significant pustular or nodular component. This is also the case for benzoyl peroxide. Antibiotics and retinoic acid derivatives are more likely to be used in severe cases. The present invention further departs from the prior art by its applicability and therapeutic efficacy across the spectrum of disease severity.

Topical application of retinoic acid also decreases comedone formation. This compound may decrease follicular epithelial cell adhesion and may beneficially modulate cellular proliferation. Unfortunately, retinoic acid is very drying and irritating to the applied area. Furthermore, retinoic acid results in an increase in photosensitivity, making it necessary for the user to diligently avoid sun exposure.

The prior art describes the topical administration of derivatives of salicylic acid. U.S. Pat. No. 4,126,681 discloses compositions and methods for topical administration of an anti-inflammatory amount of acetylsalicylic acid to inflamed tissue. U.S. Pat. No. 4,665,063 discloses a composition and a method for the treatment of dermatological disorders by topically applying acetylsalicylic acid within a carrier. U.S. Pat. No. 4,933,330 discloses a composition and method for use in the treatment of psoriasis comprising 4-aminosalicylic acid or 5-aminosalicylic acid. The prior art employs these agents because they are anti-inflammatory; they do not address any of the other etiologic factors in acne. Incorporation of salicylate compounds into acne preparations has been suggested in order to improve the activity of the therapeutic ingredient. U.S. Pat. No. 5,019,567 discloses the use of quaternary ammonim lipophilic salicylate compounds to increase the stability of benzoyl peroxide and retard its decomposition. U.S. Pat. No. 4,299,826 discloses the use of a variety of penetration-enhancing agents for topical erythromycin compositions including benzyl and ethyl salicylate. U.S. Pat. No. 5,559,098 discloses the use of alkyl salicylate compounds to increase the lipophilicity of erythromycin in topical formulations.

Additionally, these compounds have drawbacks. Allergic reactions to acetylsalicylic acid are common, particularly in individuals with asthma, eczema and other allergic conditions. A disadvantage to using either 5-aminosalicylic acid or 4-aminosalicylic acid is that these compounds are chemically unstable on exposure to air and light, which results in shortened shelf life of the product. Furthermore, the *U.S. Pharmacopia National Formulary,* United States Pharmacopeial Convention, Inc., Rockville, Md., pp. 89–92 (1994) explicitly states that a prepared solution of 5-aminosalicylic acid or 4-aminosalicylic acid should not be used after 24 hours following preparation or if the product becomes discolored. Both are decarboxylated to the light-sensitive dye m-aminophenol. Since these compounds become easily discolored upon exposure to air and light, staining can occur of objects (e.g., clothes, linens, vanities) that contact either the compound or skin that has been treated with the compound. This is clearly pharmaceutically and cosmetically unacceptable. Moreover, it appears that the metabolism of 5-aminosalicylic acid to anionic salicylate does not occur in vivo; therefore, 5-aminosalicylic acid is not considered a true salicylate. (G. K. McEvoy, Ed., *AHFS Drug Information,* Section 56:40, p. 2434, American Society of Hospital Pharmacists, Inc., Bethesda, Md. (1998).)

There is a need for a method for treating and preventing excessive sebum production and abnormal keratinocyte proliferation with a topical agent, which is not keratolytic and caustic (thereby inhibiting the sebum production and abnormal keratinocyte proliferation) to inhibit skin disorders associated with these conditions. The present invention satisfies this need and overcomes the deficiencies of prior art treatments.

Salicylate salts and derivatives are extensively used in the oral form for the treatment of fever, pain and inflammation.

This is based on their ability at therapeutic doses to inhibit prostaglandin synthesis. The prior art recognizes the use of topical salicylate containing compounds only as sunscreens (e.g., octyl salicylate) and anti-rheumatic agents (e.g., methyl salicylate).

The present invention is based on the discovery that anionic salicylate has the ability to prevent and treat acne and other skin disorders associated with the production of excessive sebum or abnormal proliferation of keratinocytes, without adversely affecting the skin at the dosage level necessary to reduce excessive sebum production or abnormal keratinocyte proliferation. The treatment may be prophylactic, palliative or curative.

SUMMARY OF THE INVENTION

One aspect of the invention relates to a method of treating a skin disorder caused by at least one of excessive sebum production and abnormal keratinocyte proliferation, the method comprising topically administering to a region of the skin of a human having a skin disorder caused by at least one of excessive sebum production and abnormal keratinocyte proliferation, a composition comprising anionic salicylate in an amount effective to reduce at least one of excessive sebum production and abnormal keratinocyte proliferation.

Another aspect of the invention relates to a method of preventing a skin disorder caused by at least one of excessive sebum production and abnormal keratinocyte proliferation, the method comprising topically administering to a region of the skin of a human susceptible to a skin disorder caused by at least one of excessive sebum production and abnormal keratinocyte proliferation, a composition comprising anionic salicylate in an amount effective to stop the occurrence or delay the occurrence of at least one of the excessive sebum production and abnormal keratinocyte proliferation.

The disclosures of all publications and patents referred to herein are hereby incorporated herein by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a photograph of a tissue paper blot of an individual's forehead immediately after cleansing with soap and water and drying, to establish a baseline for sebum production.

FIG. 2 is a photograph of a tissue paper blot of the forehead of same individual as in FIG. 1 without any treatment to the forehead 4 hours after cleansing with soap and water and drying, to establish a no-treatment control.

FIG. 3 is a photograph of a tissue paper blot of the forehead of same individual as in FIG. 1 at 4 hours after treatment with 10% anionic salicylate to the forehead according to the present invention.

FIG. 4 is a photograph of a tissue paper blot of the forehead of same individual as in FIG. 1 at 4 hours after treatment with 10% acetylsalicylic acid to the forehead for comparison purposes with FIGS. 2 and 3.

FIG. 5 is a photograph of a tissue paper blot of the forehead of same individual as in FIG. 1 at 4 hours after treatment with 2% salicylic acid to the forehead for comparison purposes with FIGS. 2 and 3.

FIG. 6 is a photograph of a tissue paper blot of the forehead of same individual as in FIG. 1 at 4 hours after treatment with 10% 5-aminosalicylic acid to the forehead for comparison purposes with FIGS. 2 and 3.

FIG. 7 is a photograph of a tissue paper blot of the forehead of same individual as in FIG. 1 at 4 hours after treatment with 50% anionic salicylate to the forehead according to the present invention.

FIG. 8 is a photograph of a tissue paper blot of the forehead of same individual as in FIG. 1 at 12 hours after treatment with 50% anionic salicylate to the forehead according to the present invention.

FIG. 9 is a photograph of a tissue paper blot of the forehead of same individual as in FIG. 1 at 24 hours after treatment with 50% anionic salicylate to the forehead according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

"Abnormal proliferation of keratinocytes" or the equivalent term "abnormal keratinocyte proliferation" as used herein means either the production of excessive keratinocytes or the abnormal differentiation of epidermal cells to keratinocytes, or both, which results in a skin disorder.

"Keratolytic" as used herein is defined as referring to an agent which results in the peeling or removal of the cornified layer of the epidermis.

"Percent" or "%" as used herein is defined in respect to components or ingredients of a compound, composition or mixture as the weight percentage of the component or ingredient based on the weight of the compound, composition or mixture containing it, unless otherwise indicated.

"Preventing" as used herein is defined as stopping the occurrence or delaying the occurrence of a skin disorder.

"Seborrheic dermatitis" as used herein is defined as chronic inflammatory disease of the skin associated with excessive sebum production.

"Treatment" as used herein is defined as eliminating, alleviating, or relieving symptoms of a skin disorder.

Description

The present invention is a method for treating or preventing a skin disorder caused by at least one of excessive sebum production and abnormal keratinocyte proliferation, the method comprising topically administering to a region of the skin of a human affected by a skin disorder or susceptible to a skin disorder caused by at least one of excessive sebum production and abnormal keratinocyte proliferation, a composition comprising anionic salicylate in an amount effective to reduce or stop the occurrence or delay the occurrence of at least one of the excessive sebum production and abnormal keratinocyte proliferation. Skin disorders treated in this invention include those associated with excessive sebum production or abnormal proliferation of keratinocytes, skin cells that synthesize keratin. Such skin disorders include, without limitation, acne, seborrhea, seborrheic dermatitis or seborrheic eczema, seborrheic adiposa or seborrheic oleosa, seborrheic sicca, keratosis pilaris, psoriasis, eczema, contact dermatitis, irritant dermatitis and ichthyosis.

The present invention is based on the discovery that anionic salicylate has the ability to prevent and treat acne and other skin disorders associated with the production of excessive sebum or abnormal proliferation of keratinocytes, without adversely affecting the skin at the dosage level necessary to reduce excessive sebum production or abnormal keratinocyte proliferation.

Anionic salicylate suppresses sebum production and keratinocyte proliferation. To the contrary, salicylic acid cannot for a number of reasons. Concentrations of salicylic acid sufficient to reduce sebum production and keratinocyte proliferation cannot be used without causing adverse effects, such as severe irritation and inflammation, to the treated area.

Pharmacologically, salicylic acid is a prodrug for anionic salicylate, since it must be converted to the ionic form in order to be metabolically active. This readily occurs in an aqueous, mildly alkaline environment such as that present in most cells. It does not occur to any significant degree in the skin due to the skin's mildly acid pH, the non-aqueous environment of the lipid-rich sebaceous glands and intercellular matrix that surrounds keratinocytes (the primary diffusion paths for the ingress of topically active agents), and salicylic acid's rapid transit time through the epithelial barrier. Salicylic acid's relatively high octanol/water partition coefficient favors partititon into the lipid rather than the aqueous compartment of skin. Topically applied salicylic acid remains a neutral solute. Therefore, for the purposes of the present invention, therapeutic efficacy requires the direct topical application of salicylate in an ionic or salt state. Anionic salicylate can be applied to the skin in extraordinarily high concentrations due to its neutral pH. This facilitates lipophilicity due to the high concentration gradient that can be attained.

The precise mechanism by which anionic salicylate is effective is not known. However, without wishing to be bound by any particular theory, the inventor believes that anionic salicylate is effective based on the following mechanisms. The pathogenesis of acne is multifactorial. Anionic salicylate possesses numerous biological properties, a number of which are relevant to the pathogenesis of acne. Anionic salicylate inhibits sebum production through two mechanisms. First, this compound inhibits lipid synthesis by inhibiting the rate limiting enzyme involved in fatty acid synthesis, acetyl CoA carboxylase. Since sebum is composed of triglycerides, free fatty acids and cholesterol, and fatty acids are the building blocks of triglycerides, preventing lipid synthesis will inhibit sebum production. Second, anionic salicylate inhibits the NADPH-dependent enzyme 5-α-reductase, which converts testosterone into its more potent metabolite, dihydrotestosterone. Dihydrotestosterone potently stimulates sebum production and sebaceous gland hypertrophy. Since the conversion to this active form of testosterone has been demonstrated to be markedly increased in individuals with acne, the inhibition of dihydrotestosterone production results in the reduction of sebum production, thereby preventing the occurrence of acne. Anionic salicylate antagonizes the epidermal growth factor receptor, as well as enzymes and transcription factors involved in DNA and RNA synthesis. This beneficially modulates cellular proliferation. By interfering with energy metabolism, it is bacteriostatic. Moreover, since anionic salicylate is a potent anti-inflammatory agent this compound ameliorates the inflammatory lesions that are characteristic of acne. Finally, anionic salicylate inhibits stress induced, catecholamine modulated lipolysis of triglycerides to irritant-free fatty acids, the reason that skin breaks out under stress.

Anionic salicylate retards comedone formation by preventing the hyperproliferation of skin cells responsible for follicular occlusion. The prior art does not recognize salicylate as being antiproliferative. Inhibition of epidermal cell growth is demonstrated by decreased comedone formation in individuals with acne. Inhibition of cellular proliferation leads to the amelioration of acne and other skin disorders characterized by abnormal proliferation of keratinocytes or fibroblasts.

The present invention exploits another biological property of anionic salicylate that makes the use of anionic salicylate a novel treatment of acne. Anionic salicylate is bacteriostatic due to its ability as noted above to uncouple oxidative phosphorylation and block bacterial energy metabolism. These bacteriostatic effects are anti-bacterial against *P. acnes*, the bacterium responsible for acne lesions. The inhibitory effect on *P. acnes* is dependent on achieving sufficiently high concentrations in the sebaceous glands where *P. acnes* resides. Topical antibiotic therapy is limited in this regard. Topical anionic salicylate overcomes this deficiency in the prior art.

The present invention is unique in that this invention exploits biologic effects of anionic salicylate that in one context, as a systemic treatment, would be toxic, but in the context of the present invention, as a topical treatment, are therapeutic, thereby going well beyond the deficiencies of the prior art treatments. The prior art does not recognize salicylate as possessing anti-seborrheic, antiproliferative and antibacterial properties. The present invention comprising the topical administration of anionic salicylate is the only single topical treatment that addresses the inflammatory, proliferative and seborrheic aspects of the skin disorders discussed above, including all of the etiologic factors in acne.

The composition of the anionic salicylate according to the present invention for treating and preventing a skin disorder may comprise at least about 0.5%, preferably about 5% to about 75%, more preferably about 10% to about 50%, and most preferably about 10% to about 20% of anionic salicylate. The concentration chosen for the anionic salicylate is based upon the condition and individual being treated and the empirical results noted for the condition and individual. It is generally desired to use the minimum effective amount, although adverse effects have not been observed for anionic salicylate even at 50% concentrations presently desired to treat seborrhea. For acne treatment, a concentration of anionic salicylate of about 10% to about 20% is presently preferred. Certain conditions may be most effectively treated even at very high concentrations, such as about 75%, of anionic salicylate.

Anionic salicylate is the dissociated product of salicylic acid, salicylsalicylic acid or a salicylate salt, namely, a salt of 2-hydroxybenzoic acid or salicylsalicylic acid, where the salicylate salt dissociates into its respective cation and anionic salicylate in aqueous solution. Anionic salicylate can also be produced by dissolving salicylsalicylic acid or salicylic acid in an alkaline aqueous medium. Preferred salicylate salts for use in the present invention include sodium salicylate, magnesium salicylate, choline salicylate, and choline magnesium trisalicylate. Salicylate salts are known compounds and are available commercially from a variety of sources.

A preferred concentration of anionic salicylate employed herein is prepared by dissolving 10 grams (g) of a salicylate salt, such as sodium salicylate, choline magnesium trisalicylate, choline salicylate, or magnesium salicylate, in enough distilled water to yield 100 g of solution (a 10% solution) of anionic salicylate. Likewise, a 20% composition of anionic salicylate, another preferred concentration, is prepared by dissolving 20 g of salicylsalicylic acid in an alkaline medium, e.g, carbonated water sufficient to yield 100 g of solution. The dissociated product, referred to herein as anionic salicylate foundation, need not be separated from and includes the respective cation of the starting material, such as magnesium from magnesium salicylate. The anionic salicylate is then mixed with the vehicle of choice depending on the particular composition desired, such as a solution, lotion or gel, cream, etc.

Suitable functional derivatives of anionic salicylate that would be pharmaceutically effective to treat the skin disor-

ders upon topical administration are also included in the present invention. Such derivatives include but are not limited to substitutions yielding salts, esters or amides or modifications of the hydroxy or carboxyl groups, such as substitutions with alkyl, aryl, alkenyl, aminoalkyl, aminoaryl, alkoxy, heteroaryl, nitro, sulpho or halogen groups.

The form of composition of the invention suitable for topical administration may be a cream, ointment, lotion, liniment, gel, solution, suspension, facial wash, paste, stick, spray, shampoo, soap, hair conditioner or powder. It may be incorporated into make-up and other cosmetics. These forms and appropriate ingredients and vehicles can be readily determined in view of this disclosure by one of ordinary skill in making pharmaceutical or cosmetic formulations. See, for example, Genaro, Ed. 1985, *Remington's Pharmaceutical Sciences,* Mack Publishing Co., Easton, Pa., for a variety of forms of topical pharmaceutical compositions that may be adapted readily to the present invention in view of this disclosure.

The pharmaceutical compositions according to the invention may comprise any suitable pharmaceutical, cosmetic or inert excipients or carriers, as well as emulsifying agents, antioxidants, buffering agents, preservatives, humectants, penetration enhancers, coloring agents, chelating agents, gel forming agents, ointment bases, pH-regulators, perfumes and skin protective agents.

Examples of suitable antioxidants which may be used in the compositions according to the invention are: butylated hydroxy anisole (BHA), butylated hydroxytoluene (BHT), ascorbic acid, sodium ascorbate, ascorbyl palmitate, nordihydroguaiaretic acid, propyl gallate, tocopherol and derivatives thereof, hydroquinones, gallic acid, sodium or potassium pyrosulphite, cysteine and cysteine derivatives.

Typical exemplary chelating agents include sodium EDTA, citric acid and phosphoric acid.

Typical exemplary gel forming agents include Carbopol® (B.F. Goodrich Co., New York, N.Y.), cellulose gum, bentonite, alginate, gelatin, polyvinylpyrrolidine (PVP), aluminum hydroxide, or Veegum® (R.T. Vanderbilt Co., New York, N.Y.).

Typical penetration enhancers include ethyl alcohol, isopropyl alcohol, propylene glycol, triethanolamine and surfactants.

Exemplary humectants include glycerin, propylene glycol, sorbitol, mannitol, urea, sodium chloride, lactic acid and xylitol.

Suitable exemplary ointment bases include beeswax, paraffin, cetyl palmitate, vegetable oil, Tween® (ICI United States, Wilmington, Del.) and Span® (ICI United States).

For topical application a pH of about 5 to about 8 is preferred. A more preferred pH is about 7.0 to about 7.5. Conventional buffering agents may be used to obtain the desired pH.

Typical exemplary preservatives include the parabens, formaldehyde, Kathon® CG (Rohm and Haas, Philadelphia, Pa.), Bronidox® (Henkel Komm. A.G., Dusseldorf, Germany), Bronopol® (The Boots Co., Ltd., Nottingham, England), p-chloro-m-cresol, chlorhexidine, benzalkonium chloride, etc.

Conventional ingredients may be used where the compositions of the invention are in the form of a shampoo or a soap, and typical soap and shampoo bases include such exemplary components as tetaine, sodium lauryl sulfate, nonyhlphenol, imidazole, sulphosuccinate, refattening agents, humectants and conditioners.

Typical exemplary solubilizers include ethyl alcohol, glycerin, isopropyl myristate, sorbitol, surfactants and oils.

Suitable exemplary suspending agents include bentonite, gelling agents, kaolin, magnesium hydroxide, agar, magnesium silicate and acacia.

Thus, variable factors in the compositions of the invention may be additives, antioxidants, chelating agents, conditioners, derivatives of the active substances, emulsifying systems, fatty-phases, gel forming agents, humectants, mass ratios, ointment bases, particle sizes, paste bases, penetration enhancers, pH, powder bases, preservatives, propellants, refattening agents, shampoo bases, solubilizers, stick bases, and suspending agents.

Other forms of anionic salicylate are also included, such as semisolid and liquid formulations. Such compositions may be formulated according to conventional pharmaceutical practices. Semisolid formulations may include gels, creams, pastes, and mixtures. Liquid formulations may include solutions, suspensions, lotions, drenches, and emulsions. Micronization of the particles is highly desirable. In some situations, liposomal delivery systems may also be preferred.

The topical administration of a composition of anionic salicylate may be an administration onto or close to the parts of the body presenting the skin disorder caused by at least one of excessive sebum production and abnormal keratinocyte proliferation, e.g., onto an exterior part of the body such as a skin surface. The application may be done simply by applying the composition onto the skin, or it may involve any device suited for enhancing the establishment of contact between the composition and the region of the skin of a human caused by at least one of excessive sebum production and abnormal keratinocyte proliferation. The composition may be impregnated or distributed onto pads, plasters, strips, gauze, sponge materials, cotton wool pieces, etc.

When the composition of anionic salicylate of the present invention is used in the treatment of a skin disorder, the amount of composition topically administered and treatment regimen will vary, depending upon the severity of the state of the skin disorder. Treatment regimes which are contemplated include a dose or dosage which is administered hourly, daily, or at any other intervals which may apply in a given case. Conventionally the composition may be applied 1 to 10 times a day, depending on the type, the severity and the localization of the skin disorder. More frequent applications would be indicated for spot resolution of active lesions, such as pustules or nodules.

When the composition of anionic salicylate is used in the topical treatment of a skin disorder, the preferred treatment will involve applying a safe and effective amount of the composition to a region of the skin of a human caused by at least one of excessive sebum production and abnormal keratinocyte proliferation. The effective dosage is about 2 to about 4 applications of the composition per day. It may be preferable to cleanse the skin prior to the treatment, and any soap or detergent composition suitable for washing the skin can be employed.

When the composition of the present invention is used in a method of preventing a skin disorder, the composition of anionic salicylate is topically administered to a region of the skin of a human that is susceptible to a skin disorder, displaying such symptoms as oily skin, excessive shine to the skin, blemishes, visible comedones. An effective dosage is about 1 to about 3 applications of the composition per day. The composition may be applied to completely normal appearing skin as well, in order to maintain this state.

The invention will be further described by reference to the following detailed Examples. These Examples are provided for purposes of illustration only, and are not intended to be

limiting unless otherwise specified. Thus, the invention should in no way be construed as being limited to the following Examples, but rather, should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

EXAMPLES

Examples 1 through 5 recite working examples of formulations of anionic salicylate.

Example 1

Composition for anionic salicylate in solution

A 10% solution of anionic salicylate was prepared by dissolving 10 g of choline magnesium trisalicylate (Trilisate™, Purdue Frederick, Norwalk, Conn.) in 87 g of distilled water. The mixture was stirred until the choline magnesium trisalicylate was fully dissolved. Each gram of choline magnesium trisalicylate yielded 587 mg of choline salicylate, 725 mg of magnesium salicylate being equivalent to 1 gram of salicylate content. Final composition:

anionic salicylate	10%
choline and magnesium	3%
water	87%

Example 2

Composition for anionic salicylate in lotion

A lotion was prepared by dissolving 4.9 g of magnesium salicylate (Doans™, Novartis, East Hanover, N.J.) in 30 ml of distilled water to produce a solution. The mixture was stirred until fully dissolved. The mixture was evaporated to form a slurry. 20.7 g of Jergens® lotion was added to the slurry to produce the following composition:

anionic salicylate	20%
moisturizing lotion	80%
magnesium cation	33.5 meq (0.3 g or 0.07%)

Example 3

Composition for anionic salicylate in solution

A 5% solution of anionic salicylate was prepared by dissolving 5 g of magnesium salicylate (Doan™, Novartis, East Hanover, N.J.) in 95 g of isopropyl alcohol 70% (w/v) to yield the following composition:

anionic salicylate	5%
isopropyl alcohol	66.5%
water	28.5%

A practitioner skilled in this art would readily recognize that other solubilizing agents could be employed depending on cosmetic or aesthetic considerations.

Example 4

Composition for anionic salicylate in lotion using salicylsalicylic acid

A lotion containing anionic salicylate was prepared by dissolving 10 g of salicylsalicylic acid (Salflex™, Carnrick, Cedar Knolls, N.J.) in 40 ml of carbonated water. The mixture was stirred until the salicylsalicylic acid was fully dissolved and allowed to evaporate to a slurry. 90 g of Jergens® (Kao Kabushiki Kaisha, Ltd., Tokyo, Japan) lotion were added to the slurry with stirring until there was a smooth consistency for the mixture, to produce the following composition:

anionic salicylate	10%
moisturizing lotion	90%

Example 5

Composition for anionic salicylate in cream

A cream containing anionic salicylate was prepared by dissolving 4.9 g of magnesium salicylate (Doans®, Ciba-Geigy Corp., Tarrytown, N.Y.) in 30 ml of distilled water. The mixture was stirred and allowed to evaporate to a slurry. The slurry was added to and mixed thoroughly with 41.4 g of Jergens® cream to produce the following composition:

anionic salicylate	10%
moisturizing cream	90%
magnesium cation	33.5 meq (0.3 g or 0.07%)

Example 6

Composition for anionic salicylate in facial wash

A facial wash containing anionic salicylate was prepared by dissolving 4.9 g of magnesium salicylate (Doans®) in 30 ml of distilled water. The mixture was stirred and allowed to evaporate to a slurry. The slurry was added to and mixed thoroughly with 41.4 g of Almay® (Revlon Consumer Products Corp., New York, N.Y.) facial cleansing cream to produce the following composition:

anionic salicylate	10%
moisturizing lotion	90%
magnesium cation	33.5 meq (0.3 g or 0.07%)

The following examples demonstrate the therapeutic efficacy of anionic salicylate for treating skin disorders according to the present invention.

Example 7

Treatment of acne with 20% topical anionic salicylate

A 47-year old male suffering from nodulocystic acne since adolescence had undergone several therapies. Benzoyl peroxide was never effective, tretinoin was helpful but was abandoned due to severe irritation and photosensitivity. Oral tetracycline was needed on almost a continuous basis resulting in good results when actively used but severe relapses occurred shortly after discontinuation. A topical anionic salicylate composition prepared from magnesium choline trisalicylate as a 20% composition in an aqueous 30% solution of isopropyl alcohol was applied to his face three times a day on an ongoing basis, which resulted in near

complete resolution of the acne. Improvement was noted within one week. Treatment was continued with twice daily application and this regimen maintained the improved state. An occasional recurrence consisted of single pustular or nodular lesions which resolved readily with additional in situ applications of the compound. For troublesome lesions the anionic salicylate composition was applied as often as 5 times a day and in a strength as high as 50% anionic salicylate. Facial oil production was markedly decreased, both visibly and palpably. Comedone formation was also markedly decreased. Discontinuing the treatment on two separate occasions resulted in prompt relapse with recurrence of all grades of acne lesions. No adverse effects, in particular, no drying, irritation or phototoxicity were experienced. To the contrary, sun exposure was well tolerated and he tanned in situations where he previously burned. After six months of treatment, the composition was replaced by a 10% lotion, then cream, with total remission of the acne which has been maintained for nine months.

Example 8

Treatment of acne with 10% aqueous choline and anionic salicylate

A 15-year old female had the typical papular/pustular lesions of acne primarily on her forehead and at times on other areas of her face, as well. A composition made using the composition of Example 1, containing 10% anionic salicylate, was applied to the affected area twice daily for 2 weeks. The lesions dried over 1 to 2 days with full resolution within 7 days. She continued to use the composition every few weeks for a few days at a time with good results. She reported a high degree of satisfaction compared to other treatments and was particularly impressed with the composition's ability to quickly remedy acute inflammatory lesions.

Example 9

Treatment of acne with 10% choline and anionic salicylate

A 13-year old female with mild comedo/papular facial acne who had never required medical attention had self-medicated herself with over the counter preparations containing either benzoyl peroxide or 2% salicylic acid. She used a composition made, using the composition of Example 1, containing 10% anionic salicylate, every few weeks for a few days at a time. Good results were obtained. She rated this treatment an equally effective alternative to the treatments used in the past.

Example 10

Treatment of seborrheic dermatitis with 20% anionic salicylate

A 44-year old female suffering from seborrheic dermatitis of the scalp was not responsive to commercial anti-seborrheic shampoos alone. She obtained good relief from topical 0.1% triamcinolone cream, a topical steroid, and used this for a number of years. A 20% solution of anionic salicylate, made following the procedure of Example 1, but with twice the amount of choline magnesium trisalicylate and 10 ml less water, was prepared. This composition, applied twice daily for 2 weeks, was substituted with efficacy equal to that of the topical steroid. She continued to use it on an as-needed basis.

Example 11

Treatment of seborrhea with 10% anionic salicylate

A 28-year old female experienced excessive facial oiliness not associated with acne since adolescence. She had always found this very cosmetically unsightly and had used numerous proprietary preparations such as astringents and facial washes. She washed her face frequently, often 5–6 times a day, and carried astringent pads in her purse. Oil free makeup only provided temporary improvement in the appearance of her complexion and had to be removed and then reapplied throughout the day. She began using a 10% solution of anionic salicylate, made using a procedure similar to Example 1, with immediate noticeable improvement. Anionic salicylate eliminated the facial shine and uncomfortable sensation of greasiness for up to 12 hours at a time. Twice daily application completely resolved the problem. She discontinued frequent washing and use of astringents with an attendant improvement in her complexion. She noted her face to be less dry and softer to the touch. On days when the solution was not applied, the oily nature of her complexion returned. She reported no unpleasant side effects from the treatment.

Example 12

A 36-year old woman suffered from nodular acne of the face since adolescence. She had never sought medical attention. She used available over-the-counter acne treatments with modest efficacy. She rarely was without visible lesions and experienced pronounced exacerbations at the time of menstruation. Treatment was initiated with a cream of 10% anionic salicylate applied twice daily. Improvement was noted within one week, and by two weeks, she was lesion-free. Her face was noted to be much less oily. Examination after one month of treatment revealed her complexion to be completely clear of acne lesions and much less oily. She has continued treatment for three months with persistent therapeutic effect. Additionally, perimenstrual breakouts have completely ceased. She has suffered none of the side effects associated with prior treatments, e.g., dryness, redness and irritation. She rates the treatment as far superior to 10% benzoyl peroxide or 2% salicylic acid.

Example 13

A 49-year old woman sought treatment because of facial blemishes. She developed acne in her early 20s for which she was treated with retinoic acid and chemical peeling. Her acne gradually improved over the next 20 years but she continued to be dissatisfied with her complexion which remained oily. Her face was easily irritated and cosmetically bothersome blemishes were usually present. She began applying a cream containing anionic salicylate, first at a concentration of 5% for two months, with an increase to 10% thereafter. Her skin became blemish-free within a month and was less oily. Over six months, she has noted a progressive improvement in skin texture and color with no apparent side effects.

Example 14

The individual in Example 6 also suffered from acne involving his back. He applied a lotion of 10% anionic salicylate to the involved region once daily which resulted in drying of active lesions within 24–48 hours and complete resolution within 7 days. The fact that the involved area was covered, and therefore inconspicuous, allowed an alternat-

ing A-B-A treatment paradigm of two weeks of treatment followed by two weeks without treatment. Treatment consistently resulted in total eradication of acne lesions. Lesions consistently recurred in the untreated state. This on-off treatment paradigm was repeated for four full cycles demonstrating a direct cause and effect relationship between treatment with anionic salicylate and resolution of acne lesions.

Example 15

Reduction of sebum on the forehead treated with anionic salicylate

This Example was performed to compare treatments of the present invention using 10% and 50% anionic salicylate according to the present invention with 10% acetylsalicylic acid, 10% 5-aminosalicylic acid and 2% salicylic acid treatments and control conditions (no treatments) to determine the effect of the treatments or lack of treatments on sebum formed on the forehead.

The 47-year old male having a history as noted in Example 7, and after 9 months of such treatment, was tested for production and reduction of sebum on the forehead using 10% anionic salicylate, 10% acetylsalicylic acid, 10% 5-aminosalicylic acid, 50% anionic salicylate or 2% salicylic acid applied separately at different times. Active treatment was discontinued for 7 days before the first test was performed.

On the following morning at 8:00 A.M., the forehead was cleansed with soap and water and patted dry, but no treatments were applied. Immediately after cleansing, a baseline tissue paper blot was obtained by applying tissue paper to the forehead for 10 seconds with mild pressure, to obtain the baseline blot as shown in FIG. 1. Four hours after cleansing, a tissue paper blot of the forehead as shown in FIG. 2 was obtained by applying tissue paper for 10 seconds with mild pressure. This represents the control condition without any treatment.

A solution containing 10% anionic salicylate was prepared, following the procedure of Example 1. Other test compositions were prepared following similar procedures but using different amounts and types of active ingredients.

The procedure for testing the various compositions for sebum reduction is as follows: Cleansing of the forehead occurred at 8:00 A.M. The forehead, a conventional measurement site for sebum production, was cleansed with soap and water and the area was patted dry. Absorbent paper or absorbent tape are conventionally used to visualize sebum production.

The next day, after the forehead was patted dry, a solution of 10% anionic salicylate was applied to the forehead. After another 4 hours, tissue paper was applied to the forehead with mild pressure to the area for 10 seconds, resulting in the blot shown in FIG. 3. Treatment was then discontinued for seven days.

On the following morning at 8:00 A.M., the forehead was cleansed again with soap and water. After the forehead was patted dry, a 10% solution of acetylsalicylic acid was applied to the forehead. Four hours after treatment with the 10% solution of acetylsalicylic acid, a tissue paper blot was obtained of the area as shown in FIG. 4 by applying tissue paper to the forehead for 10 seconds with mild pressure. After the test with 10% acetylsalicylic acid, the individual resumed using the 10% anionic salicylate for a few weeks. The individual again stopped all treatments for 7 days.

At 8:00 A.M. the following day, the forehead was cleansed again with soap and water and the area was patted dry. A 2% solution of salicylic acid which was impregnated on a commercially available pad (Stri-Dex®, Blistex Inc., Oak Brook, Ill.) was applied to the forehead. Four hours after treatment, a tissue paper blot of the treated area as shown in FIG. 5 was obtained by applying tissue paper to the forehead for 10 seconds with mild pressure.

The same procedure was followed for the tests with 10% 5- aminosalicylic acid and 50% anionic salicylate each after a seven day period of no treatments. The forehead was cleansed with soap and water, patted dry, and the 10% solution of 5-aminosalicylic acid was applied. A 4-hour blot was then obtained (FIG. 6). Maintenance treatment with 10% anionic salicylate was resumed. To test the possibility of a dose-effect relationship, 50% anionic salicylate was used as the test solution. Tissue paper blots were obtained at 4, 12 and 24 hours after application (FIGS. 7, 8 and 9, respectively).

A photocopy was made of each blot. Since sebum is opaque, light transmission varies with the amount of sebum present. The results of the treatments were compared to the baseline and the control, wherein the baseline is a tissue paper blot of the forehead of the same individual immediately after cleansing with soap and water (FIG. 1) and the control is the tissue paper blot of the forehead of same individual without any treatment to the forehead 4 hours after the start of the test (FIG. 2). The tissue paper blots were compared by visually inspecting the density of the dark area representing the absorption of sebum by the tissue paper. Greater sebum absorption, resulting from greater sebum production, produced a darker area and a larger area of darkness. The size and density of the blots after treatment with anionic salicylate were markedly reduced. The density was much less and the size of the blots was much smaller for the treatments with anionic salicylate after 4 hours (FIG. 3) in contrast to the tissue paper blot of the forehead treated with 10% acetylsalicylic acid (FIG. 4), the tissue paper blot of the forehead treated with 2% salicylic acid (FIG. 5) and the tissue paper blot of the forehead treated with 10% 5-aminosalicylic acid (FIG. 6), which have greater density of dark areas and larger sizes. The application of anionic salicylate on the forehead (FIG. 3) effectively reduced the presence of sebum, compared to no treatment (FIG. 2) and to the treatment with the 10% acetylsalicylic acid (FIG. 4), 2% salicylic acid (FIG. 5) and 10% 5-aminosalicylic acid (FIG. 6). FIG. 7 (50% anionic salicylate) demonstrates nearly complete suppression of sebum production at 4 hours, with persistence but with some gradual diminution of this effect at 12 and 24 hours (FIGS. 8 and 9, respectively). The results of these studies demonstrate the effectiveness of the treatment of the present invention in controlling sebum compared to the control blot or to any other treatments. Visual inspection demonstrates no effect on sebum production of 10% acetylsalicylic acid (FIG. 4), 2% salicylic acid (FIG. 5) or 10% 5-aminosalicylic acid (FIG. 6) when compared to the control blot (FIG. 2).

It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but is intended to cover modifications within the spirit and scope of the present invention as defined by the appended claims.

What is claimed is:

1. A method of treating or maintaining remission of a skin disorder caused totally or in part by the excessive production of sebum with a topical composition whereby the topical composition contains anionic salicylate or a precursor com-

pound able to ionize anionic salicylate applied to areas of human skin that excrete excessive amounts of sebum wherein such composition is able to decrease sebum production and thereby, beneficially affect the disorder in question.

2. The method of claim 1 where the composition contains anionic salicylate or a precursor compound able to ionize to anionic salicylate.

3. The method of claim 1 where the precursor compound of anionic salicylate is freely soluble in water as defined by a log octanol/water partition coefficient of less than 1.

4. The method of claim 1 where the precursor compound of anionic salicylate freely dissociates in water as defined by a solubility product constant (K_{sp}) where the exponent is positive and the degree of ionization is complete or nearly complete.

5. The method of claim 1 where the precursor compound is a salt of salicylic acid.

6. The method of claim 1 where the precursor compound salt of salicylic acid is preferably chosen from the group consisting of magnesium salicylate, choline salicylate, choline magnesium trisalicylate, sodium salicylate, zinc salicylate, manganese salicylate or copper salicylate.

7. The method of claim 1 where the skin disorder is acne.

8. The method of claim 1 where the skin disorder is seborrhea.

9. The method of claim 1 where the skin disorder is seborrhea sicca.

10. The method of claim 1 where the skin disorder is seborrheic dermatitis.

11. A method of treating or maintaining remission of a skin disorder caused totally or in part by the excessive proliferation of keratinocytes with a topical composition whereby the topical composition contains anionic salicylate or a precursor compound able to ionize anionic salicylate applied to areas of human skin where excessive keratinocyte proliferation occurs wherein the composition is able to decrease the proliferation of keratinocytes.

12. The method of claim 1 where the composition contains anionic salicylate or a precursor compound able to ionize to anionic salicylate.

13. The method of claim 1 where the precursor compound of anionic salicylate is freely soluble in water as defined by a log octanol/water partition coefficient of less than 1.

14. The method of claim 1 where the precursor compound of anionic salicylate freely dissociates in water as defined by a solubility product constant (K_{sp}) where the exponent is positive and ionization is complete or nearly complete.

15. The method of claim 1 where the precursor compound is a salt of salicylic acid.

16. The method of claim 1 where the precursor compound salt of salicylic acid is preferably chosen from the group consisting of magnesium salicylate, choline salicylate, choline magnesium trisalicylate, sodium salicylate, zinc salicylate, manganese salicylate or copper salicylate.

17. The method of claim 9 where the skin disorder is acne.

18. The method of claim 9 where the skin disorder is psoriasis.

19. The method of claim 9 where the skin disorder is eczema.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Bohn et al.

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USE OF 1-HYDROXY-2-PYRIDONES FOR THE TREATMENT OF SEBORRHEIC DERMATITIS

DECLARATION OF MITCHELL S. WORTZMAN, Ph.D.

I, Mitchell S. Wortzman, hereby declare as follows:

1. I am the Executive Vice President, Research and Development for Medicis Pharmaceutical Corporation ("Medicis"), and have been employed by Medicis since 1997. From 1980 to 1997, I was employed at Neutrogena Corporation, and was the President of the Dermatologics Division starting in 1989.

2. Medicis is a licensee under this patent application.

3. Since 1980 I have been involved in the research and development for numerous dermatological products. My Ph.D. is in cellular and molecular biology from the University of Southern California.

4. I have reviewed the record in this application concerning the differences between dandruff and seborrheic dermatitis. The scientific literature of record correctly

states the understanding in the fields of dermatology and dermatological research that these are separate and distinct conditions. See, the reference cited previously in the above-identified application and attached as Exhibits A.

5. The rest of the scientific literature is in accord with the view that dandruff is a "noninflammatory" scaling of the scalp, while "seborrheic dermatitis is an inflammatory, erythematous, and scaling eruption that occurs in seborrheic areas...such as the scalp, face, and trunk." (See Manual of Dermatologic Therapeutics, Fifth ed., p. 164-167 (1995) attached as Exhibit B).

6. Even the scales of dandruff look different from the scale from seborrheic dermatitis; dandruff has thin, white or gray flakes, while seborrheic dermatitis has oily, yellowish scales with inflammation. (See Handbook of Nonprescription Drugs, p. 550-552 (1996) attached as Exhibit C).

7. One of ordinary skill in the art would not find it obvious to use a certain composition to treat seborrheic dermatitis, merely because the same composition is used to treat dandruff.

8. I am unable to respond to the Examiner's position to the contrary. The Examiner has not addressed the substance of the cited literature, and does not appear to speak on the basis of her own research or clinical experience. Without any basis for her rejection of the well-settled understanding of those in the art, I cannot know why she has taken this mistaken position, how to explain the source of her error, or what evidence would convince her that her position is incorrect. The most that one can say is that the Examiner appears to have taken a position on the

basis of her own belief that is contrary to the scientific literature of record and my own long experience in the field.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application and any registration resulting therefrom.

Mitchell S. Wortzman, Ph.D.

Date: 6/6/03

EXHIBIT A

CHAPTER 126 - Seborrheic Dermatitis

Gerd Plewig
Thomas Jansen

Seborrheic dermatitis is a common, chronic papulosquamous dermatosis that is usually easily recognized. It affects infants and adults and is often associated with increased sebum production (seborrhea) of the scalp and the sebaceous follicle-rich areas of the face and trunk. The affected skin is pink, edematous, and covered with yellow-brown scales and crusts. The disease has a wide range from mild to severe, including psoriasiform or pityriasiform patterns and erythroderma.[1,2,3,4,5] Seborrheic dermatitis is one of the most common skin manifestations in patients with HIV infection.[6,7,8,9] It is therefore included in the spectrum of premonitory lesions and should be carefully evaluated in high-risk patients.

Incidence

Seborrheic dermatitis has two age peaks, one in infancy within the first 3 months of life and the second around the fourth to the seventh decade of life. No data are available on the exact incidence of seborrheic dermatitis in infants, but the disorder is common. The disease in adults is believed to be more common than psoriasis, for example, affecting at least 2 to 5 percent of the population. Men are affected more often than women in all age groups. There does not appear to be any racial predilection. Seborrheic dermatitis is one of the most common diseases associated with HIV infection as it is found in up to 85 percent of these patients.[7]

Etiology and Pathogenesis

Although many theories abound, the cause of seborrheic dermatitis remains unknown.

Seborrhea

The disease is associated with oily-looking skin (seborrhea oleosa), although increased sebum production cannot always be detected in these patients.[10] Even if seborrhea does provide a predisposition, seborrheic dermatitis is not a disease of the sebaceous glands. The high incidence of seborrheic dermatitis in newborns parallels the size and activity of the sebaceous glands at this age. It has been shown that newborns have large

sebaceous glands with high sebum secretion rates.[11] In childhood, sebum production and seborrheic dermatitis are closely connected. In adulthood, however, they are not, as the sebaceous gland activity peaks in early puberty and seborrheic dermatitis may not occur until decades later.

The sites of predilection—face, ears, scalp, and upper part of the trunk—are particularly rich in sebaceous follicles. Two diseases are prevalent in these regions: seborrheic dermatitis and acne. In patients with seborrheic dermatitis, the sebaceous glands are often particularly large on cross-sectional histologic specimens. In one study, skin surface lipids were not elevated but the lipid composition was characterized by an increased proportion of cholesterol, triglycerides, and paraffin and a decrease in squalene, free fatty acids, and wax esters.[12] Seborrheic dermatitis seems to be more frequent in patients with parkinsonism, in whom sebum secretion is increased, and after treatment with levodopa and a reduction of skin oiliness, seborrheic dermatitis may be improved.[13]

The synonym *eczéma flannellaire* stems from the idea that a retention of skin surface lipids by clothing—cotton (flannel), wool, or synthetic underwear in particular—promotes or aggravates seborrheic dermatitis.

Microbial Effects

Unna and Sabouraud, who were among the first to describe the disease, favored an etiology involving bacteria, yeasts, or both. This hypothesis has remained unsupported, although bacteria and yeasts can be isolated in great quantities from affected skin sites.

In infancy, *Candida albicans* is often found in dermatitic skin lesions and in stool specimens. Intracutaneous tests with candidin, positive agglutinating antibodies in serum, and positive lymphocyte-transformation tests in affected infants revealed a sensitization to *C. albicans*. Even so, these observations cannot be convincingly linked to the pathogenesis. Aerobic bacteria were recovered from the scalp of patients with seborrheic dermatitis (geometric mean of 140,000/cm^2 versus 280,000 in normal individuals and 250,000 in persons with dandruff). In contrast, *Staphylococcus aureus* was rarely seen in normal persons or those with dandruff. When present, it was recovered in about 20 percent of patients with seborrheic dermatitis, accounting for an average of about 32 percent of the total skin flora.[14]

Propionibacterium acnes counts were low in patients with seborrheic dermatitis (7550 geometric mean/cm^2 in those without dandruff). The

small quantities of *P. acnes* in patients with seborrheic dermatitis may explain the low yield of free fatty acids from their skin surfaces.

The lipophilic yeast *Pityrosporum* is abundant in normal skin (504,000 geometric mean/cm^2 versus 922,000 in individuals with dandruff and 665,000 in patients with seborrheic dermatitis).[14] This organism has received particular attention in recent years. Some authors claim strong evidence in favor of a pathogenic role for these microbes,[15,16,17] whereas others do not share this view. Their arguments are that *P. ovale* is not the causative organism but is merely present in large numbers. Clearing of seborrheic dermatitis by selenium sulfide and continued suppression of *P. ovale* with topical amphotericin B caused a relapse of the disease on inflamed scalp skin.[17] In seborrheic dermatitis, both normal[18] and high[19] levels of serum antibodies against *P. ovale* have been demonstrated. A cell-mediated immune response to *P. ovale* has been found in normal individuals using *Pityrosporum* extracts in lymphocyte-transformation studies.[20] Others have demonstrated an association between strong skin colonization with *P. ovale* and altered cellular immunity.[21] Overgrowth of *P. ovale* may lead to inflammation, either through introduction of yeast-derived metabolic products into the epidermis or as a result of the presence of yeast cells on the skin surface. The mechanism of production of inflammation would likely then be through Langerhans cell and T lymphocyte activation by *Pityrosporum* or its byproducts. When *P. ovale* comes into contact with serum, it can activate complement via the direct and alternative pathways, and this may play some part in the introduction of inflammation.[22]

Miscellaneous

Drugs

Several drugs have been reported to produce seborrheic dermatitis–like lesions, including arsenic, gold, methyldopa, cimetidine, and neuroleptics.[23,24]

Neurotransmitter abnormalities

Seborrheic dermatitis is often associated with a variety of neurologic abnormalities, pointing to a possible influence of the nervous system.[25,26] These neurologic conditions include postencephalitic parkinsonism, epilepsy, supraorbital injury, facial paralysis, unilateral injury to the ganglion of Gasser, poliomyelitis, syringomyelia, and quadriplegia. Emotional stress seems to aggravate the disease; a high rate of seborrhea is reported among combat troops in times of war.

Physical factors

Seasonal variations in temperature and humidity are related to the course of the disease. Low autumn and winter temperatures and low humidity in centrally heated rooms are known to worsen the condition. Seborrheic dermatitis of the face was observed in 8 percent of 347 patients receiving PUVA therapy for psoriasis and occurred within a few days to 2 weeks after the beginning of treatment[12]; the patients had no previous history of facial psoriasis or seborrheic dermatitis. Lesions were avoided by masking the face during irradiation.

Aberrant epidermal proliferation

Epidermal proliferation is increased in seborrheic dermatitis, like psoriasis, which explains why cytostatic therapeutic modalities may improve the condition.[13]

Nutritional Disorders

Zinc deficiency in patients with acrodermatitis enteropathica and acrodermatitis enteropathica–like conditions may be accompanied by dermatitis mimicking seborrheic dermatitis of the face. Seborrheic dermatitis, however, is not associated with zinc deficiency nor does it respond to supplementary zinc therapy. Seborrheic dermatitis in infancy may have a different pathogenesis. Biotin deficiency, whether secondary to a holocarboxylase deficiency or a biotinidase deficiency, and abnormal metabolism of essential fatty acids[12] have been proposed as possible mechanisms.

Immunodeficiency and Seborrheic Dermatitis

The development of seborrheic dermatitis either de novo or as a flare of preexisting disease may also serve as a clue to the presence of HIV infection. The first report of this association in 1984[6] was followed by observations from all parts of the world.[7,8,9] The expression of the disease differs in several aspects from the classic form seen in HIV-seronegative individuals (Figs. 126-1, 126-2, 126-3, and 126-4). The distribution is extensive, severity remarkable, and treatment often difficult (Fig. 126-5). Even the histologic changes differ somewhat from those seen in commonly encountered seborrheic dermatitis (Table 126-1).[9]

The increased incidence and severity of seborrheic dermatitis in HIV-seropositive individuals has led to speculation that unchecked growth of *Pityrosporum* in immunosuppressed patients is responsible. However,

studies that compared quantitative *Pityrosporum* cultures in AIDS patients with and without seborrheic dermatitis either failed to demonstrate increased yeast colonization in patients with seborrheic dermatitis[20] or yielded only a weak correlation between yeast colonization and seborrheic dermatitis.[21]

Psoriasis and Seborrheic Dermatitis

In patients with a psoriatic diathesis, particularly adults, seborrheic dermatitis is said to evolve into psoriasis. The term *sebopsoriasis* is sometimes used for these overlapping conditions. It should be used with caution because psoriasis, especially of the scalp, is clinically and histologically almost indistinguishable from seborrheic dermatitis.

Pityriasis Amiantacea

Pityriasis amiantacea (also known as tinea amiantacea, porrigo amiantacea, tinea asbestina, fausse teigne amiantacée, keratosis follicularis amiantacea) is the name given to a disease of the scalp in which heavy scales extend onto the hairs and separate and bind together their proximal portions (Fig. 126-6).

Pityriasis amiantacea is a reaction of the scalp, often without evident cause, that may occur at any age. It may be observed as a complication or sequel of streptococcal infection, seborrheic dermatitis, atopic dermatitis, or lichen simplex and it also occurs in psoriasis, of which it may be the first clinical manifestation.[22,23] The process may be circumscribed or diffuse. It is only slightly inflammatory, with dry, micaceous scales, or markedly inflammatory, with admixture of a crust. Removal of the scales reveals normal or erythematous, edematous epidermis. The process is not followed by atrophy, scarring, or alopecia. If scarring alopecia occurs, it may be related to secondary infection.

A common form complicates chronic or recurrent fissuring behind one or both ears, mostly in young girls, with the sticky scales extending several centimeters into the neighboring scalp. Another form extends upward from patches of lichen simplex and is seen mainly in middle-aged women.

Histopathology

The histologic picture varies according to the stage of the disease, i.e., acute, subacute, or chronic.[24,25,26] In acute and subacute seborrheic dermatitis, there is a sparse superficial perivascular infiltrate of lymphocytes and histiocytes, slight to moderate spongiosis, slight psoriasiform

hyperplasia, follicular plugging by orthokeratosis and parakeratosis, and scale-crusts containing neutrophils at the tips of the follicular ostia (see Table 126-1). In chronic seborrheic dermatitis, there are markedly dilated capillaries and venules in the superficial plexus in addition to the above-mentioned features.

Clinically and histologically, the lesions of chronic seborrheic dermatitis are psoriasiform and often difficult to distinguish from those of psoriasis.[24] Abortive forms of psoriasis share many features with seborrheic dermatitis. There are lesions that resemble psoriasis and may persist over many years before they finally turn into overt psoriasis. The most important diagnostic signs of seborrheic dermatitis are mounds of scale-crust containing neutrophils at the tips of the dilated horn-filled follicular infundibula. Acrosyringia and acroinfundibula may be plugged by corneocyte casts.

The most consistent findings in pityriasis amiantacea are spongiosis, parakeratosis, migration of lymphocytes into the epidermis, and a variable degree of acanthosis.[33] The essential feature responsible for the asbestos-like scaling are diffuse hyperkeratosis and parakeratosis together with follicular keratosis surrounding each hair by a sheath of corneocytes and debris.

Exfoliative Cytology

Cytologic abnormalities of superficial horny cells (corneocytes), including ortho- and parakeratotic (nucleated) cells, horny cells in different stages of nuclear decomposition (halo cells), and masses of leukocytes, can be evaluated by exfoliative cytology. Seborrheic dermatitis and psoriasis, however, present similar findings compared with other conditions of the dermatitis-eczema group.[17]

Clinical Findings

In all patients with seborrheic dermatitis there is a so-called seborrheic stage, often combined with a gray-white or yellow-red skin discoloration, prominent follicular openings, and mild to severe pityriasiform scales. Several forms can be distinguished (Table 126-2).

Seborrheic Dermatitis in Infants

The disease occurs in infants, predominantly within the first months of life, as an inflammatory disease mainly affecting the hairy scalp and intertriginous folds with greasy-looking scales and crusts. Other regions such as the

center of the face, chest, and neck may also be affected. Scalp involvement is fairly characteristic. The frontal and parietal scalp regions are covered with an oily-looking, thick, often fissured crust [*crusta lactea* (*milk crust*), or *cradle cap*]. Hair loss does not occur, and inflammation is sparse. In the course of the disease, the redness increases and the scaled areas form clearly outlined erythematous patches topped by a greasy scale. Extension beyond the frontal hairline occurs. The retroauricular folds, the pinna of the ear, and the neck may also be involved. Otitis externa is often a complicating factor. Semiocclusive clothing and diapers favor moisture, maceration, and intertriginous dermatitis, particularly in the folds of the neck, axillae, anogenital area, and groin. Opportunistic infection with *C. albicans*, *S. aureus*, and other bacteria occurs. The clinical aspect reminds one of psoriasis vulgaris, hence the expressions *psoriasoid psoriasis* or *napkin psoriasis*.[38]

Course

The disease is usually protracted over weeks to months. Exacerbation and, rarely, erythroderma desquamativum may occur. The prognosis is good. There is no indication that infants with seborrheic dermatitis are more likely to suffer from the adult form of the disease.

Differential Diagnosis

The differential diagnosis in seborrheic dermatitis of infancy includes atopic dermatitis (which usually starts after the third month of life); psoriasis in newborns, a rare disease; scabies; and Langerhans cell histiocytosis. The most useful distinguishing feature between atopic dermatitis and seborrheic dermatitis is the increased number of lesions on the forearms and shins in the former and in the axillae in the latter. The development of skin lesions solely in the diaper area favors a diagnosis of infantile seborrheic dermatitis.[32] Radioallergosorbent testing for egg white and milk antibodies or other geographically or ethnically relevant allergens (e.g., soybean) and, to a lesser extent, total IgE levels may be useful in diagnosing atopic dermatitis at an early stage and distinguishing it from infantile seborrheic dermatitis.[40]

Erythroderma Desquamativum (Leiner's Disease)

This complication of seborrheic dermatitis in infants (dermatitis seborrhoides infantum) was described in 1908 by Leiner.[41] There is usually a sudden confluence of lesions leading to a universal scaling redness of the

skin (erythroderma). The young patients are severely ill with anemia, diarrhea, and vomiting. Secondary bacterial infection is common. The disease occurs in both a familial and a nonfamilial form. Patients with the former are noted for having a functional deficiency of C5 complement, resulting in defective opsonization. These patients respond to antibiotics and infusions of fresh-frozen plasma or whole blood.

Seborrheic Dermatitis in Adults

The clinical picture and course of this disease differ in adults and infants.

Seborrheic eczematid is the mildest form of the disease (eczematid = eczema-like, dermatitis-like). It is associated with seborrhea, scaling, mild redness, and often pruritus of the scalp, eyebrows, nasolabial folds, and retroauricular area, as well as over the sternum and the shoulder blades (see Figs. 126-1 to 126-4). Asymptomatic, fluffy white dandruff of the scalp represents the mild end of the spectrum of seborrheic dermatitis and has been referred to as *pityriasis sicca.*

Erythema paranasale, more common in young women than men, may be part of this disease spectrum.

Patchy seborrheic dermatitis is the classic, well-known disease with chronic recurrent lesions. Lesions have a predilection for scalp, temples, retroauricular folds and external ear canals (Fig. 126-3), inner parts of the eyebrows and glabella with nasolabial folds (Fig. 126-2), and V-shaped areas of the chest and back (*eczema mediothoracicum*). Less frequently, intertriginous areas such as the side of the neck, axillae, submammary region, umbilicus, and genitocrural folds are involved. Skin lesions are characterized by a yellow color, mild to severe erythema, mild inflammatory infiltrate, and oily, thick scales and crusts. This has occasionally been referred to as *pityriasis steatoides.* Patients report pruritus, particularly on the scalp and in the ear canal. The lesions start with follicular and perifollicular redness and mounds; they spread until they form clearly outlined, round to circinate (petaloid) patches (Greek *petalon,* a thin plate or leaf). The pityriasiform type of seborrheic dermatitis is seen on the trunk and mimics the lesions of pityriasis rosea, producing oval scaly lesions whose long axes tend to parallel the ribs. In some individuals only one or two sites are involved. Chronic otitis externa may be the sole manifestation of seborrheic dermatitis. Another possible manifestation is blepharitis, with honey-colored crusts along the rim of the eyelid and casts of horny cell debris around the eyelashes. In men, a more follicular type of seborrheic

dermatitis may extend over large parts of the back, flanks, and abdomen.

Course

Usually the disease lasts for years to decades with periods of improvement in warmer seasons and periods of exacerbation in the colder months. Widespread lesions may occur as a result of improper topical treatment or sun exposure. The extreme variant of the disease is a generalized exfoliative erythroderma (seborrheic erythroderma).

Differential Diagnosis

The differential diagnosis varies from site to site: *scalp*: dandruff, psoriasis, atopic dermatitis, impetigo; *ear canal*: psoriasis or contact dermatitis, irritant or allergic; *face*: rosacea, contact dermatitis, psoriasis, impetigo; *chest and back*: pityriasis versicolor, pityriasis rosea; *eyelids*: atopic dermatitis, psoriasis, *Demodex folliculorum* infestation (demodicosis, demodicidosis); *intertriginous areas*: psoriasis, candidiasis.

Therapy

In general, therapy is directed toward loosening and removal of scales and crusts, inhibition of yeast colonization, control of secondary infection, and reduction of erythema and itching. Patients should be informed about the chronic nature of the disease and understand that therapy works by controlling the disease rather than by curing it.

Infants

Scalp

Treatment consists of the following measures: removal of crusts with 3 to 5% salicylic acid in olive oil or a water-soluble base; warm olive oil compresses; application of low-potency glucocorticoids (e.g., 1% hydrocortisone) in a cream or lotion for a few days; mild baby shampoos; proper skin care with emollients, creams, and soft pastes.

Intertriginous Areas

Treatment measures include drying lotions, such as 0.2 to 0.5% dioquinol in zinc lotion or zinc oil. In cases of candidiasis, nystatin or amphotericin B lotion or cream can be applied followed by soft and stiff pastes. In cases of oozing dermatitis, application of 0.1 to 0.25% gentian violet (solutio pyoctanini) in combination with cotton or muslin diapers is often helpful. Imidazole preparations (e.g., 2% ketoconazole in soft pastes, creams, or

lotions) may also be effective.

Adults

Because the disease runs an unpredictably long course, careful and mild treatment regimens are recommended. Anti-inflammatory agents and, when indicated, antimicrobial or antifungal agents have to be used.

Scalp

Daily shampoo with shampoos containing 1 to 2.5% selenium sulfide, antifungals (e.g., ketoconazole), zinc pyrithione, benzoyl peroxide, salicylic acid, coal or juniper tar, or detergents is recommended. Crusts or scales can be removed by overnight application of glucocorticoids or salicylic acid in water-soluble bases or, when necessary, under occlusive dressings. Tinctures, alcoholic solutions, hair tonics, and similar products usually aggravate the inflammatory state and should be avoided.

Face and Trunk

Patients should avoid greasy ointments and reduce or omit the use of soaps. Alcoholic solutions or pre- or aftershave lotions should not be recommended. Low-potency glucocorticoids (1% hydrocortisone is usually sufficient) are helpful early in the course of the disease; uncontrolled long-term applications will lead to side effects such as steroid dermatitis, steroid rebound phenomenon, steroid rosacea, and perioral dermatitis.

Antifungals

Good results are achieved with topical application of antifungal agents, especially imidazoles. Usually 2% preparations in the form of shampoos and creams are used. Double-blind studies report 75 to 95 percent improvement. In these trials, however, only ketoconazole[42,43,44,45,46] or itraconazole[43] were studied; other imidazoles such as econazole, clotrimazole, miconazole, oxiconazole, isoconazole, and ciclopiroxolamine may also be effective. Allylamine antifungals such as terbenafine solution (1%) may also be effective.[47] Comparative studies are lacking. The authors' personal experience, though based on open, uncontrolled studies only, is best with ketoconazole cream. Imidazoles, like other antifungal agents, have a wide spectrum of effects, including anti-inflammatory properties and inhibition of cell wall lipid synthesis.[16] Their efficacy is not proof of a causal relationship between *P. ovale* and seborrheic dermatitis.

Metronidazole

Topical metronidazole is a worthwhile alternative in the treatment repertoire of seborrheic dermatitis. It has made its successful debut in patients with rosacea. Extemporaneous formulations (up to 2% in a cream base) or commercial products (0.75% gel, MetroGel) are used once or twice daily. There are no formal studies, and the drug is registered for the treatment of rosacea only. This recommendation is based on the authors' experience.

Seborrheic Otitis Externa

Seborrheic otitis externa can be best treated with a low-potency glucocorticoid cream. Many otic preparations (solutions) contain neomycin, which is a strong sensitizer, and should therefore be avoided. Once dermatitis is under control, the glucocorticoid should be discontinued and a solution containing aluminum acetate be applied once or twice daily to maintain control. This acts as a drying agent and reduces the microbial flora.

Seborrheic Blepharitis

Special consideration is given to the treatment of seborrheic blepharitis. The use of hot compresses with gentle debridement with a cotton-tipped applicator and baby shampoo one or more times daily is recommended. Stubborn cases may require the use of a topical antibiotic such as sodium sulfacetamide ophthalmic ointment. The possible use of ocular preparations containing glucocorticoids should be referred to an ophthalmologist.

Pityriasis Amiantacea

The scales should be removed by the use of cade oil (juniper tar) ointment or a topical tar/salicylic ointment. Either preparation should be washed out of the scalp after 4 to 6 h with a suitable shampoo, e.g., tar or imidazole shampoo. Potent topical glucocorticoid scalp creams or liquids may be beneficial in some cases, preferably under plastic occlusion in the initial phase. A vitamin D analogue (calcipotriol cream or lotion, or tacalcitol ointment) is also recommended and useful in selected patients. If topical treatment fails, systemic glucocorticoids (e.g., 0.5 mg prednisolone per kg body weight daily for about 1 week) in combination with topical treatment (steroid under occlusion, followed by open application) is worthwhile. Concomitant antimicrobial treatment (e.g., macrolides, sulfonamides) is reserved for stubborn cases, especially if bacterial coinfection of the scalp is

treatment of tinea pedis can help to prevent the development of a life-threatening cellulitis. Intertrigo needs to be prevented as it can be a portal of entry for irritants and infectious agents. Prevention of venous ulcers and of allergic contact dermatitis needs to be meticulous in patients with gravitational eczema who are dangerously prone to both of these complications. Elderly skin is more prone to traumatic lacerations. Aged skin which is edematous is particularly susceptible to trauma and bulla formation.

Skin Atrophy

Skin atrophy can be compounded due to a poor understanding of the correct use of medications, leading to misuse of topical steroids in the elderly patient, who may have associated edema with vascular insufficiency. The geriatric dermal-epidermal interface is already compromised. The fragile skin of the poorly groomed foot is a setup for fissures, bullae, infection, and further loss of the ability to be mobile.

Seborrheic Dermatitis

(See Chap. 126)

Although seborrheic dermatitis can affect all ages and both males and females, it becomes much more common with increasing age. The association with increasing age correlates best in men, whereas women have a peak in morbidity after puberty, after which it gradually declines. There appears to be a cephalocaudad progression of the location with increasing age. Although the face and head are the predominant sites in younger age groups and certainly can be severely affected in the elderly, genitocrural and lower extremity lesions increase with age. The pubis, crural folds, gluteal cleft, and penis (seborrheic balanitis) may be involved. Lesions may be misdiagnosed as tinea infections. Striking flares of seborrheic dermatitis have been associated with confining illnesses such as coronary infarction. Exacerbations may eventuate in a diffuse erythroderma, which is often misdiagnosed. Pathogenesis may be related to changes in the cutaneous microflora. A neurophysiologic role is suggested by the association of seborrheic dermatitis with mental retardation and with Parkinson's disease. Seborrheic dermatitis may appear abruptly in the elderly, heralding the onset of Parkinson's disease. The scalp is usually involved, often giving rise to a mistaken diagnosis of dandruff. Simple dandruff declines late in adult life.

Intertrigo

Intertrigo is more frequent in the elderly due to redundant skin folds and environmental factors, including temperature, moisture, friction, and inadequate hygiene. Polymicrobial secondary colonization and subsequent infection can occur. No one organism can be singled out as the main agent.

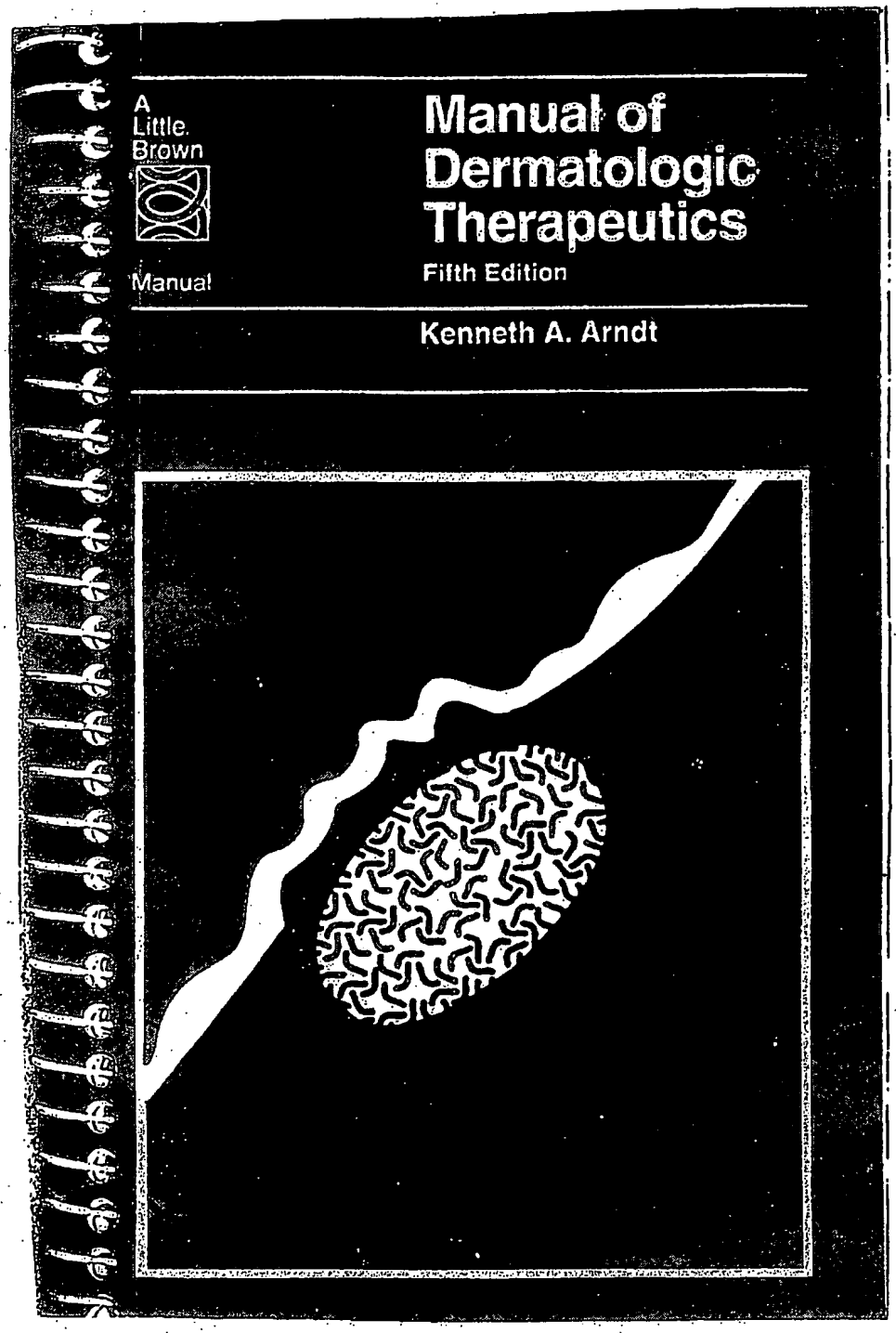
Treatment of the Cutaneous Signs of Aging

Multiple medical and surgical therapeutic modalities are evolving for the treatment of the outward signs of intrinsic aging and photoaging. See Table 146-3.

Some publications still use the obsolete term *premature skin aging* to describe alterations in unprotected skin, notably the face and sun-exposed areas, implying that this is merely exaggerated manifestations of normal aging. However, the evidence is convincing that photoaging is not simply an acceleration of the inevitable age-dependent alterations. Photoaging denotes the gross and microscopic cutaneous changes that are a consequence of chronic solar radiation. Recent studies demonstrate that this spectrum of changes is often diametrically opposed to that which occurs in intrinsically aged skin.[4,64,65] Sun worshippers do look prematurely aged, and this is the basis for the common misconception. Those who scrupulously avoid the sun can reach the ninth decade with smooth, unblemished skin that shows only mild thinning, loss of elasticity, and a deepening of normal expression lines. By contrast, at age 50, serious sun worshippers, especially those of skin phototype I (blue-eyed, fair-skinned, Celtic ancestry who burn easily and tan poorly), have a plethora of wrinkles, with yellowed, lax, dry, leathery, knobby, blotchy skin and a variety of benign, premalignant, and malignant neoplasms.

Late nineteenth century dermatologists, notably Unna and Dubreuilh, clearly recognized the baleful influence of sunlight by comparing the integument of farmers and sailors to that of indoor workers. This was at a time when the leisured class stayed out of the sun. Today, a tan is prized by Caucasians and is ironically equated with health and beauty. Because decades of extensive sun bathing can occur before the photoaging changes become apparent to the naked eye,[12] there is a lack of urgency concerning prevention. This latent period also reinforces the impressions that actinically damaged skin differs only quantitatively from intrinsic aging. However, photoaging has distinctive and unique features that are quite different from normal aging.

EXHIBIT B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Brown
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Manual of
Dermatologic
Therapeutics
Fifth Edition
Kenneth A. Arndt

29 Seborrheic Dermatitis and Dandruff

I. **Definition and pathophysiology.** Seborrheic dermatitis and dandruff may each cause a scaling on the scalp that is often associated with itching. There are, however, distinctions that can be found between the two disorders. Dandruff is noninflammatory, increased scaling on the scalp that represents the more active end of the spectrum of physiologic desquamation. On a normal scalp, approximately 487,000 cells/sq cm can be found after a detergent scrub; scalps affected with dandruff and seborrheic dermatitis liberate up to 800,000 cells/sq cm.

Seborrheic dermatitis is an inflammatory, erythematous, and scaling eruption that occurs primarily in "seborrheic" areas, i.e., those with a high number and activity of sebaceous glands, such as the scalp, face, and trunk. Although seborrheic dermatitis occurs in neonatal and postpubertal life—times during which sebaceous glands are most active—no direct relationship between the amount or composition of sebum and the presence of dermatitis has been documented. Patients produce no more sebum on their scalps than do controls, and reducing sebum excretion affects neither dandruff nor seborrheic dermatitis. This disease is one of accelerated epidermal growth resulting in retention of nuclei in stratum corneum cells that have not had sufficient time to completely mature. On a normal scalp there are approximately 3700 nucleated cells/sq cm; on scalps with dandruff there are 25,000, and on those with seborrheic dermatitis the count is 76,000. Follicular occlusion may be a primary event, with yeast overgrowth in the folliculitis associated with seborrheic dermatitis.

It has been postulated that prolonged retention of sebum on the skin may in some way act as an irritant or alter epidermal function following its percutaneous reentry. *Pityrosporum ovale*, a lipophilic yeast which is a normal inhabitant of the skin, has been hypothesized to be the etiologic agent in seborrheic dermatitis. There is a significantly increased incidence—and often particular severity—of seborrheiclike dermatitis in patients with AIDS (Grossler, 1989; Marino, 1991). More direct support comes from reports that seborrheic dermatitis responds to oral and topical ketoconazole, an imidazole effective against *Pityrosporum* (see sec. IV.F). No evidence of immediate or delayed hypersensitivity reactions to *P. ovale* has been demonstrated in seborrheic dermatitis. Higher than normal total serum IgG or IgA level has been found in some patients. Often noted and equally intriguing is the increased incidence of seborrheic dermatitis in Parkinson's disease (idiopathic and drug-induced) and other neurologic disorders; one study demonstrated improvement in 10 patients with the use of isotretinoin, implicating an increase in the residual sebum pool due to immobility. *P. ovale* has been cultured in 73% of infants with seborrheic dermatitis; the yeast may be cultured from the scalp, face, and presternal or inguinal region.

II. **Subjective data.** The lesions of seborrheic dermatitis and dandruff are often asymptomatic, but pruritus is not uncommon and may be intense at times.

III. **Objective data**

A. Dandruff appears simply as noninflammatory, diffuse scaling on the scalp only.

B. With seborrheic dermatitis, there is erythema, scaling, and at times exudation; the borders may be well defined. Mild erythema and fine, dry scaling also may be found on the eyebrows, eyelids, nasolabial and postauricular folds, moustache, beard, and presternal areas. Inframammary folds, groin, gluteal crease, and umbilicus are also affected. Lesions may become thick, semiconfluent, yellow, and greasy. Secondary impetiginization and folliculitis may occur. Seborrheic dermatitis may be a cause of a generalized exfoliative erythroderma.

C. Seborrheic marginal blepharitis, which consists of erythema and scaling of eyelid margins and cilia, is often associated with mild granular conjunctivitis. Seborrheic dermatitis in other sites is often not present.

D. Infantile seborrheic dermatitis is characterized by erythema and scaling plaques involving the scalp, diaper region, or flexural surfaces; when the vertex of the scalp is involved, the condition is know as cradle cap. Generalized exfoliative dermatitis in an infant secondary to seborrheic dermatitis is referred to as Leiner's syndrome with or without a defect in the fifth component of complement.

E. Drug eruptions from gold therapy may mimic seborrheic dermatitis, as may a vitamin B–deficient diet.

IV. **Therapy**

A. Agents effective in eliminating the scaling of dandruff and seborrheic dermatitis appear to act by varying mechanisms. Selenium sulfide (see Chap. 40, Cleansing Agents, sec. I.F.2) and tars (see Chap. 40, Keratolytic, Cytotoxic, and Destructive Agents, sec. XVII) inhibit mitotic activity, and selenium kills yeasts as well. Zinc pyrithione (see Chap. 40, Cleansing Agents, sec. I.F.3) is directly cytotoxic and has antimicrobial effects, and salicylic acid (see Chap. 40, Keratolytic, Cytotoxic, and Destructive Agents, sec. XIV) disrupts the bonds that cause stratum corneum cells to stick together. There are no studies comparing the efficacies of antiseborrheic shampoos. The following agents are listed in rough approximation of usefulness:

1. Ketoconazole (Nizoral) shampoo is used at least twice weekly.
2. Shampoos containing 2½% selenium sulfide (Selsun) should be applied 2–3 times weekly for 5–10 minutes each time.
3. Preparations containing 1–2% zinc pyrithione (Danex, DHS-Zinc, Head and Shoulders, Zincon) work almost as well.
4. Salicylic acid–sulfur shampoos (Ionil, Sebulex) are less effective but show definite activity.
5. Tar shampoos (DHS-T, Ionil T, Pentrax, Sebutone, T/Gel, Zetar) inhibit epidermal proliferation through cytostatic effects after an initial burst of transient hyperplasia.
6. Chlorodine (Capitrol) shampoo contains a synthetic antibacterial compound similar to the hydroxyquinoline compounds used in dermatology for many years. Comparative efficacy studies with this shampoo are unavailable.
7. Any nonmedicinal shampoo, particularly those containing surfactants and detergents, will remove scales and lead to subjective clinical improvement and decreased desquamation for about 4 days. These agents should be used every 2 days to control dandruff.

B. If the lesions are extensive or very inflammatory, also have the patient apply either a topical corticosteroid solution, lotion, or spray. (Valisone or Diprosone lotion is generally effective; Synalar or Lidex solution and other corticosteroid lotions are also useful.) Alternatively, a 10% sodium sulfacetamide lotion bid–tid may be used.

C. **Ketoconazole (Nizoral)**, an imidazole with action against *P. ovale*, has been reported effective for seborrheic dermatitis when given either orally (200 mg PO daily), topically (2% cream applied bid), or as a 2% shampoo. Topical ketoconazole has been studied in children and shown to be effective and well tolerated. Its efficacy is approximately equivalent to that of 1% hydrocortisone cream. Oral ketoconazole has too many potential adverse reactions to warrant its use in this condition.

D. Thick crusts may be removed more easily by overnight applications of a keratolytic gel, with or without plastic cap occlusion: 3% sulfur, 3% salicylic acid, 4% cetyl alcohol–coal tar distillate (Pragmatar) cream; Baker's P&S liquid; 20-10-5 ointment (see Chap. 27, sec. V.B.6) or a 30-minute compress with warm mineral oil prior to shampooing.

E. Seborrheic dermatitis lesions on other areas respond rapidly to a corticosteroid cream such as 1% hydrocortisone applied 1–3 times a day. Aerosols or lotions are easier to apply to hairy areas. Prolonged application of high-potency fluorinated corticosteroids may lead to disfiguring telangiectasia and atrophy. Other useful topical agents for glabrous skin include sulfur-containing medications such as 10% sulfacetamide lotion; 3% sulfur, 3% salicylic acid, 4% cetyl alcohol–coal tar distillate (Pragmatar) cream; or formulations such as precipitated sulfur 3–10%, salicylic acid 1–5%, and tar 2% in an ointment base or 1–3% sulfur in calamine lotion.

F. Seborrheic blepharitis is treated 1–3 times a day with either sulfacetamide alone or a 10% sulfacetamide, 0.2% prednisolone, 0.12% phenylephrine suspension (Blephamide, Vasocidin) or similar preparations (Cetapred, Metimyd, Optimyd). It is essential to monitor intraocular tension concurrent with intermittent or chronic steroid therapy in or around the eye.

G. Topical lithium succinate ointment used daily for 8 weeks showed remission or marked improvement compared with placebo in 30 patients with seborrheic dermatitis; it is presumed to act as an anti-inflammatory agent.

H. A 15% propylene glycol solution applied to the scalp reduced the number of *P. ovale* and improved seborrheic dermatitis in 90% of those treated.

I. Ultraviolet light (both UVA and UVB) are inhibitory to the growth of *P. ovale*. Many individuals note improvement of seborrheic dermatitis during the summer months.

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EXHIBIT C

Handbook of Nonprescription *Drugs*

Published by
American Pharmaceutical Association
The National Professional Society of Pharmacists
2215 Constitution Avenue, NW
Washington, DC 20037

should be avoided in intertriginous areas because of their maceration potential. Also, in an acute process, ointments may cause further irritation because of their occlusive effect.
- Aerosols, gels, or lotions may be recommended when the dermatitis affects a hair-covered area of the body.

A large number of cosmetic dry skin formulations are commercially available. These may contain natural oils, vitamins, or a variety of fragrances that have a psychologic appeal. However, the fragrances and dyes found in many of these formulations may be irritating or allergenic to sensitive dry skin and should be avoided.

Efficacy of any skin care product may need to be sacrificed or compromised somewhat to achieve patient acceptance. The most efficacious product that the patient will accept should be recommended.

Topical nonprescription products come in various package sizes and strengths. Table 3 lists the amount of drug needed to cover a given area of the body three times daily over a 1-week period. By being aware of such details, the pharmacist can serve the patient economically as well as therapeutically.

Scaly Dermatoses

Dandruff, seborrheic dermatitis (seborrhea), and psoriasis are described as chronic, scaly dermatoses. They may be placed on a spectrum ranging from dandruff, a minor problem that is primarily cosmetic, to psoriasis, a clinical condition that can have significant physical, psychologic, and economic consequences. (See Table 4 for the distinguishing features of these three dermatoses.)

Part of the body	Cream/ointment (g)	Lotion/solution/gel (mL)
Face	5–10	100–120
Both hands	25–50	200–240
Scalp	50–100	200–240
Both arms or both legs	100–200	240–360
Trunk	200	360–480
Groin and genitalia	15–25	120–180

Adapted from Bingham EA. Topical dermatologic therapy. In: Rook A, Parish LC, Beare JM, eds. *Practical Management of the Dermatologic Patient.* Philadelphia: JB Lippincott; 1986: 227–8.

Nonprescription products are appropriate for all degrees of dandruff. Many cases of seborrheic dermatitis will respond to the same nonprescription drug regimen used to treat dandruff. Psoriasis that involves mild inflammation may be responsive to nonprescription treatment. However, initial diagnosis and management of acute flare-ups require the attention of a physician.[29]

Specific Conditions

Dandruff

Dandruff is a chronic, noninflammatory scalp condition that results in excessive scaling of scalp epidermis. Dandruff is clinically visible in approximately 20% of the population. Severity declines in the summer and is not proved to be aggravated by emotional states. Authorities disagree over whether inadequate shampooing exacerbates dandruff; however, there is agreement that a consistent washing routine is important in managing the condition.[29,30]

Etiology and Characteristics Dandruff is not a true disease; rather, it is a physiologic event and condition much like the growth of hair and nails, except that the end product is visible on the scalp and has a substantial cosmetic and social stigma associated with its presence. It correlates with the proliferative activity of the epidermis. Dandruff generally appears at puberty, reaches a peak in early adulthood, levels off in middle age, and declines in advancing years (occurring only rarely after age 75).

Dandruff is characterized by accelerated epidermal cell turnover, an irregular keratin breakup pattern, and the shedding of cells in large scales. It is normal for epidermal cells on the scalp to continually slough off just as they do on other parts of the body. It is also normal for the epidermal cell turnover rate to be greater on the scalp than on other parts of the body. In dandruff patients, however, the epidermal cell turnover rate on the scalp is about twice that of normal scalp.[7] This rate also assists in distinguishing dandruff from seborrhea and psoriasis; psoriasis has a higher rate than seborrhea, which has a higher rate than dandruff.

Dandruff is diffuse rather than patchy; it is not inflammatory; and pruritus is common. Scaling, the only visible manifestation of dandruff, is the result of an increased rate of horny substance production on the scalp and the sloughing of large scales. Dandruff scales often appear around a hair shaft because of the epithelial growth at the base of the hair. This phenomenon does not occur on the normal scalp because the horny substance breaks up in a much more uniform fashion. The horny layer of the scalp normally consists of 25–35 fully keratinized, closely coherent cells per square millimeter arranged in an orderly fashion. However, in dandruff, the intact horny layer has fewer than 10 normal cells per square millimeter, and nonkeratinized cells are common. With dandruff, crevices occur deep in the stratum corneum, resulting in cracking, which generates relatively large scales. If the large scales are broken down to smaller units, the dandruff becomes less visible.

As the rate of keratin cell turnover increases, so too

	Dandruff	Seborrhea	Psoriasis
Location	Scalp	Adults and children: head and trunk Children only: back, intertriginous areas	Scalp, elbows, knees, trunk, and lower extremities
Exacerbating factors	Generally a stable condition, exacerbated by inadequate washing, dry climate	Exacerbated by many external factors, notably stress and low relative humidity	Exacerbated by mechanical irritation, stress, climate, drugs, infection, endocrine factors
Appearance	Thin, white, or grayish flakes; even distribution on scalp	Patchy lesions with margins; mild inflammation; oily, yellowish scales	Usually symmetrical, red, patchy plaques with sharp border; silvery-white scale; small bleeding points when removed. Difficult to distinguish from seborrhea in early stages or in intertriginous zones
Inflammation	Absent	Present	Present
Epidermal hyperplasia	Absent	Present	Present
Epidermal kinetics	Turnover rate is two times faster than normal	Turnover rate is about five to six times faster than normal	Turnover rate is about five to six times faster than normal
Percentage of incompletely keratinized cells	Rarely exceeds 5% of total corneocyte count.	Commonly makes up 15–25% of corneocyte count	Commonly makes up 40–60% of corneocyte count

Information extracted from:
Wright DE. In: Clark C, ed. *Self-Medication: A Reference for Health Professionals.* 3rd ed. Ottawa: Canadian Pharmaceutical Association; 1988: 87.
McGinley KJ et al. *J Invest Dermatol.* 1969; 53: 107.
Kligman AM et al. *J Soc Cosmet Chem.* 1974; 25: 73.

does the number of incompletely keratinized cells, a situation characterized by the retention of nuclei in keratin layer cells. Incompletely keratinized cells in dandruff appear in clusters, possibly as a result of tiny inflammatory foci that are incited when capillaries discharge a load of inflammatory cells into the epidermis, causing accelerated epidermal growth in a small area. These microfoci are found on all scalps but are increased proportionately in dandruff.[7]

The specific cause of accelerated cell growth seen in dandruff is unknown. There is continuing debate over whether dandruff is a result of elevated microorganism levels—particularly of the yeast *Pityrosporum ovale.*[30]

Treatment Dandruff is more of a cosmetic than a medical problem, and treatment is fairly straightforward. The patient needs to understand that there is no direct cure for dandruff and that the condition can usually be well controlled. Washing the hair and scalp with a nonmedicated shampoo every other day or even daily is often sufficient to control dandruff. If it is not, medicated nonprescription antidandruff products may be recommended. With medicated shampoos, contact time improves effectiveness. The patient should be counseled to allow medicated shampoo to remain on the hair for approximately 1 minute before rinsing and repeating. Thorough rinsing is important in the use of all shampoo products.

A cytostatic agent such as pyrithione zinc, selenium sulfide, or coal tar is recommended. These agents reduce the epidermal turnover rate. However, the coal tar–containing shampoos may tend to discolor light hair as well as clothing and jewelry and thus may not appeal to some patients. Next, a keratolytic shampoo containing salicylic acid or sulfur may be used. If dandruff proves resistant to these agents, the patient should be referred to a physician for treatment.[29,31]

Seborrheic Dermatitis

Seborrheic dermatitis is a general term for a group of eruptions that occur predominantly in the areas of greatest sebaceous gland activity (eg, the scalp, face, and trunk). This condition affects approximately 12 million Americans. Seborrhea occurs mostly in middle-aged and elderly persons, particularly men. It is often found in persons with parkinsonism, endocrine states associated with obesity, zinc deficiency, and human immunodeficiency virus infection. Quadriplegics and persons who have experienced a cerebrovascular accident (stroke) or a myocardial infarct (heart attack) also seem prone to seborrhea. Because nonprescription therapy is effective in a significant percentage of cases, the pharmacist can play a key role in the management of seborrhea.[32]

Etiology and Characteristics Seborrhea is marked by accelerated epidermal proliferation and sebaceous gland activity.[19] The distinctive characteristics of the disorder are its common occurrence in hairy areas (especially the scalp); the appearance of dull, yellowish-red lesions, which are well demarcated; and the associated presence of oily-appearing, yellowish scales. Pruritus is common.[33] The most common form, seborrhea of the scalp, is characterized by greasy scales on the scalp that often extend to the middle third of the face with subsequent eye involvement. (See color plates, photograph 10.) Lesions may also appear in the external auditory canal and around the ear. When seborrhea of the scalp occurs in newborns and infants, it is referred to as cradle cap and is treated primarily by gentle massaging with baby oil followed by a nonmedicated shampoo to remove the scales. Pruritus does not appear to accompany cradle cap, and the condition often clears spontaneously by 8–12 months of age.[11,29,32]

The cause of seborrhea is unknown although predisposition appears to be a genetic trait. Emotional and physical stress serve as aggravating factors. Proposed etiologic factors have included vitamin B complex deficiency, food allergies, autoimmunity, climate changes, and low relative humidity. The characteristic accelerated cell turnover and enhanced sebaceous gland activity give rise to the prominent scale displayed in the condition; however, there is no clear-cut quantitative relationship between the degree of sebaceous gland activity and susceptibility to seborrhea.

It is almost universally accepted that seborrhea is merely an extension of dandruff, and the controversy regarding the involvement of *P ovale* extends to seborrhea. Some researchers, however, dispute the link with dandruff, offering evidence that seborrhea is a separate condition. Incompletely keratinized cells commonly make up 15–25% of the corneocyte count in seborrheic dermatitis but rarely exceed 5% in dandruff.[7,32]

Assessment The differential assessment of seborrheic dermatitis is usually straightforward. However, whereas dandruff is considered a relatively stable condition, seborrhea fluctuates in severity, often as a result of stress. Involvement of eyebrows and eyelashes, with concurrent blepharitis, is associated with seborrhea but not with dandruff. Moreover, dandruff is considered a noninflammatory condition whereas seborrhea is usually accompanied by erythema and sometimes crusting.

Lesion distribution is a key factor in distinguishing seborrhea from psoriasis. Seborrhea commonly involves the face and generally is not found on the extremities, whereas psoriasis is rarely found on the face but is commonly found on bony prominence such as the elbows and knees. However, the scalp is generally involved in both conditions, and if this is the only site of involvement, differential assessment is difficult. Physical appearance of scales may help to differentiate the two disorders. Seborrhea is usually marked by oily, yellow scales whereas psoriatic scales are generally dry and silvery in appearance. Additionally, the presence of the Auspitz sign (small bleeding points) is indicative of psoriasis.

Fungal infections may be mistaken for seborrhea. Thus, proper assessment is important because fungal infections may be worsened by seborrhea therapy using hydrocortisone. If the lesion is located in the groin, tinea cruris (jock itch) must be considered, especially during warm weather. Scalp lesions must be evaluated for the possibility of tinea capitis (ringworm of the scalp).[7]

Treatment The treatment of seborrheic dermatitis is similar to that of dandruff. Seborrhea generally responds to shampoos containing pyrithione zinc, selenium sulfide, salicylic acid, or coal tar. However, frequent use of selenium sulfide may make the scalp oily and may actually exacerbate the seborrheic condition.

A primary difference between the treatment of dandruff and that of seborrhea is the use of topical corticosteroids. These products are not indicated for dandruff but may be used in the management of seborrheic dermatitis whenever erythema is persistent after therapy with medicated shampoos. Hydrocortisone lotions for scalp dermatitis are available without a prescription. The patient should be instructed to apply the hydrocortisone product two to three times a day until symptoms subside and then intermittently to control acute exacerbations. The patient should also be instructed in the proper technique of application. The hair should be parted and the product applied directly to the scalp and massaged in thoroughly. This process should be repeated until desired coverage of the affected area is achieved. The absorption of medication into the scalp is enhanced if the lotion is applied after shampooing; skin hydration promotes drug absorption.

The patient should be encouraged to minimize prolonged and continued use of hydrocortisone in the treatment of seborrheic dermatitis because a rebound flare may occur when prolonged therapy is discontinued. If the condition worsens or if symptoms persist for more than 7 days, a physician should be consulted. At this point, a more potent topical steroid may be indicated.[7]

If the seborrhea spreads to the ear canal, eyelashes, or eyelids, a physician should be consulted for appropriate therapy. This may include the use of prescription otic and ophthalmic agents.

Nonprescription products used to treat seborrhea are to be avoided for children under 2 years of age, except under the advice and supervision of a physician.[34]

Psoriasis

Psoriasis is estimated to afflict 1–3% of the US population. Lesions are often localized but may become gener-

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

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Paper No. 46

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MANFRED BOHN, KARL THEODOR KRAEMER, and ASTRID MARKUS

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BOARD OF PATENT APPEALS AND INTERFERENCES

Appeal No. 2004-0309
Application No. 09/077,194

HEARD: June 22, 2004

Before WINTERS, MILLS, and GREEN, Administrative Patent Judges.

WINTERS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the examiner's final rejection of Claims 38-42, 48, and 53 -66, which are all the claims pending in U.S. Application No. 09/077,194.

Introduction

Claims 38, 39, 41, 42, 48, 53, 54, and 56-66 stand rejected under 35 U.S.C. § 103(a) as unpatentable in view of the combined teachings of Durrant et al. (Durrant),

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U.S. Patent No. 4,699,924, issued on October 13, 1987; and Lange, U.S. Patent No. 5,132,107, issued on July 21, 1992. Claims 40 and 55 stand rejected under 35 U.S.C. § 103(a) as unpatentable in view of the combined teachings of Durrant; Lange; and Saint-Leger, U.S. Patent No. 5,650,145, issued July 22, 1997, based on Application No. 08/435,806, filed May 5, 1995.

We have considered applicants' specification and claims, the applied prior art, and the positions of the examiner and applicants on appeal. On consideration of the record as a whole, we find that neither Durrant nor Lange constitutes the closest prior art. Saint-Leger, which was only applied against two dependent claims by the examiner, is the closest prior art. Accordingly, we vacate the examiner's rejections under 35 U.S.C. § 103(a).[1] We also enter the evidence submitted with applicants' Reply Brief received June 9, 2003, including the Declaration of Mitchell S. Wortzman, Ph.D, and exhibits A, B, and C attached thereto: A) Gerd Plewig & Thomas Jansen, Dermatology in General Medicine, 5th ed., CD-ROM (1999); B) Kenneth A. Arndt, Manual of Dematologic Therapeutics, 5th ed. (1995); and C) Handbook of Nonprescription Drugs (American Pharmaceutical Association, Washington DC 1996).[2]

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[1] As stated in Ex parte Zambrano, 58 USPQ2d 1312, 1313 (Bd. Pat. App. & Interf. 2001), "[t]he term 'vacate,' as applied to an action taken by an appellate tribunal, means to set aside or to void. When the Board vacates an examiner's rejection, the rejection is set aside and no longer exists" (footnote omitted).

[2] The exhibits attached to the Declaration of Mitchell S. Wortzman, Ph.D, will be cited herein as Exhibits A, B, or C. All references to page numbers of those exhibits are taken literally from the pagination provided by applicants.

We note applicants' commentary respecting commercial success during the hearing on June 22, 2004, but find no objective evidence of record in support thereof. As discussed more fully infra, we enter new grounds of rejection under the provisions of 37 CFR § 41.50(b).

The Claims

A correct copy of pending claims 38-42, 48, and 53-66 is found in Appendix B attached to applicants' Appeal Brief received December 16, 2002 (Paper No. 33).

Claim 39, the broadest claim on appeal, is directed to a method for treating a human or animal patient in need of treatment for seborrheic dermatitis by administering an effective amount of a composition comprising (1) at least one 1-hydroxy-2-pyridone having formula (I) and (2) at least one surfactant selected from anionic surfactants, cationic surfactants, nonionic surfactants, and amphoteric surfactants.

Claim 38 differs from claim 39 by adding a limitation that the composition has a pH ranging from about 4.5 to about 6.5.

Claim 40 depends from claim 38 and adds the limitation "in which the at least one 1-hydroxy-2-pyridone of formula (I) comprises a cyclohexyl radical in the R^4 position."

Claim 48 depends from claim 38 and adds the limitation "in which the pharmaceutical composition further comprises at least one additional surfactant chosen from anionic, cationic, nonionic, and amphoteric surfactants."

Claim 59 is directed to a method for treating a human or animal patient in need of treatment for seborrheic dermatitis by administering an effective amount of a composition comprising (1) at least one 1-hydroxy-2-pyridone having formula (I), (2) at least one surfactant selected from anionic surfactants, cationic surfactants, nonionic surfactants, and amphoteric surfactants, and (3) at least one keratolytic agent.

Claim 61 depends from claim 59 and adds the limitation "in which the at least one 1-hydroxy-2-pyridone of formula (I) comprises a cyclohexyl radical in the R^4 position."

Claim 53 is identical to Claim 59 except for an additional requirement limiting the composition to a pH ranging from about 4.5 to about 6.5.

Claim 55 depends from claim 53 and adds the limitation "in which the at least one 1-hydroxy-2-pyridone of formula I comprises a cyclohexyl radical in the R^4 position."

Claim 66 is directed to a method for treating a human or animal patient in need of treatment for seborrheic dermatitis by administering an effective amount of a composition comprising (1) at least one 1-hydroxy-2-pyridone having formula (I), (2) at least one surfactant selected from anionic surfactants, cationic surfactants, nonionic surfactants, and amphoteric surfactants, and (3) lactic acid.

Claim 65 is essentially identical to Claim 66 except for an additional requirement limiting the composition to a pH ranging from about 4.5 to about 6.5.

Claim Interpretation

The claimed inventions are directed to methods for treating a patient in need of treatment for seborrheic dermatitis. We interpret the phrase "treating a human or animal patient in need of treatment for seborrheic dermatitis" as treating a patient afflicted with any form of seborrheic dermatitis for any one or more of the symptoms associated with that disorder.

We are mindful that applicants' specification defines seborrheic dermatitis as follows (Specification, p. 1, l. 3-7):

> Seborrheic dermatitis is understood as meaning a disorder of the scalp which differs from simple dandruff by the presence of erythema as a sign of inflammation, by the greater degree of scaling with occasional itching and burning, and by the occurrence of eczematous changes to other body sites.

Although seborrheic dermatitis may differ from simple dandruff in symptomatic degree or kind, nonetheless, applicants' claims are directed to methods "for treating a human or animal patient in need of treatment for seborrheic dermatitis" (emphasis added to claim language). Giving the claim language its broadest reasonable interpretation consistent with the specification, we conclude that patients in need of treatment for seborrheic dermatitis reasonably may be treated for dandruff or any one or more of the other symptoms associated with seborrheic dermatitis. See In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989)("During patent examination the pending claims must be interpreted as broadly as their terms reasonably allow"). Therefore, a prior art method that describes treating a patient for at least one symptom associated

with seborrheic dermatitis is construed to anticipate or render obvious a method for treating a patient in need of treatment for seborrheic dermatitis.

Seborrheic dermatitis is characterized by a variety of symptoms. The disorder is often associated with increased sebum production (seborrhea). (Exhibit A, page 1). Other symptoms may include: patchy lesions with margins, mild inflammation, and oily, yellowish scales. (Exhibit C, page 551).

Symptoms of seborrheic dermatitis range in degree from mild to severe. Although symptoms can be severe, "[a]symptomatic, fluffy white dandruff of the scalp represents the mild end of the spectrum of seborrheic dermatitis and has been referred to as pityriasis sicca." (Exhibit A, page 8). Thus, fluffy white flakes of the scalp are associated with both seborrheic dermatitis and simple dandruff. It follows that (1) treating dandruff, viz., fluffy white flakes, also constitutes treating a symptom of seborrheic dermatitis; and (2) an invention for treating dandruff would likely be useful for treating at least one symptom of seborrheic dermatitis. In fact, "[m]any cases of seborrheic dermatitis will respond to the same nonprescription drug regimen used to treat dandruff." (Exhibit C, page 550, column 2, lines 2-4).

Applicants submitted the declaration of Mitchell S. Wortzman with their Reply Brief. Wortzman concludes that "[o]ne of ordinary skill in the art would not find it obvious to use a certain composition to treat seborrheic dermatitis, merely because the same composition is used to treat dandruff." (Declaration of Mitchell S. Wortzman,

page 2, seventh paragraph). Again, we emphasize that the claimed invention is not directed to a method for successfully treating every symptom associated with, or eradicating, seborrheic dermatitis. Nor is it directed to a method of treating a human or animal patient having the classic, well-known disorder of patchy seborrheic dermatitis. (Exhibit A, page 8). The claimed invention is directed to a method for treating a patient "in need of treatment for seborrheic dermatitis." It cannot be gainsaid that "[m]any cases of seborrheic dermatitis will respond to the same nonprescription drug regime used to treat dandruff." (Exhibit C, page 550, column 2, lines 2-4).

New Grounds of Rejection

I. 35 U.S.C. § 102

Claim 39 is rejected under 35 U.S.C. § 102 as anticipated by Saint-Leger. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros., Inc. v. Union Oil Co., 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir.), cert. denied, 484 U.S. 827 (1987). "The reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it." In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990).

Saint-Leger is directed to a method for treating a human patient with a mixture of antifungal and antibacterial compounds. Saint-Leger states (column 2, lines 17-23):

> According to the invention, by the term 'antifungal agent' is intended any substance capable of inhibiting or preventing the growth of yeasts, in particular those found at the surface of the epidermis which is rich in sebaceous glands and especially at the surface of the scalp such as, for example, Pityrosporum ovale and varieties thereof (Pityrosporum orbiculare and Malassezia furfur).

Controlling the growth of Pityrosporum ovale appears to treat a symptom of seborrheic dermatitis. "Pityrosporum ovale, a lipophilic yeast which is a normal inhabitant of the skin, has been hypothesized to be the etiologic agent in seborrheic dermatitis." (Exhibit B, page 164). "Overgrowth of P. ovale may lead to inflammation." (Exhibit A, page 3). Therefore, controlling the growth of that microorganism appears to treat a symptom of seborrheic dermatitis.

In Example 6, Saint-Leger describes a method for treating a male human patient with a composition applied to the scalp, resulting in a change in the seborrhoea. Saint-Leger discloses that "individuals evaluated the variations in their seborrhoea, which could be increased, stable or reduced" (column 6, lines 23 and 24). Table II shows the results of that variation in seborrhoea. Many of the individuals experienced reduced seborrhoea or stable seborrhoea . (Id.). Therefore, Saint-Leger is directed to a method for treating a human patient with at least one symptom of seborrheic dermatitis. We here note that the active ingredients in the composition of Example 6, OCTOPIROX and IRGASAN, are the same active ingredients in the composition of Example 1 of that reference.

Example 1 of Saint-Leger discloses a method which fully meets the method recited in claim 39 using a specified 1-hydroxy-2-pyridone as active ingredient and an

anionic surfactant. Example 1 describes a method of treating a human patient with a shampoo comprising sodium lauryl ether sulfate containing 2.2 mol of ethylene oxide and 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2-(1H)-pyridone, i.e., OCTOPIROX. (Saint-Leger, column 4, Example 1). Applicants' invention recited in claim 39 is directed to a method of treating a human or animal patient in need of treatment for seborrheic dermatitis by administering an effective amount of a composition comprising at least one 1-hydroxy-2-pyridone having formula (I) and at least one surfactant which may be an anionic surfactant. On this record, applicants do not deny that the 1-hydroxy-2-pyridone described by Saint-Leger in Example 1 is a species within the genus of compounds having formula (I) recited in claim 39. Further, applicants' specification teaches that anionic surfactants are preferred for use in the invention; and that examples of anionic surfactants include, inter alia, fatty alcohol ether sulfates that can be used in the form of water-soluble or water-dispensable salts, e.g., the sodium salt (specification, page 6, lines 4-6 and lines 18-31). Thus, Saint-Leger describes the composition recited in claim 39 comprising sodium lauryl ether sulfate and a specific 1-hydroxy-2-pyridone for use in treating a symptom of seborrheic dermatitis.[3]

II. 35 U.S.C. § 102 or 35 U.S.C. § 103

Claims 38-42 and 48 are rejected under 35 U.S.C. § 102 as anticipated by or, in the alternative, under 35 U.S.C. § 103 as unpatentable over Saint-Leger.

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[3] As stated in In re Ruscetta, 255 F.2d 687, 689-690, 118 USPQ 101, 104 (CCPA 1958), "it is axiomatic that the disclosure of a species in a reference is sufficient to prevent a later applicant from obtaining generic claims."

Example 1 of Saint-Leger anticipates claim 39. However, claim 38 adds a pH limitation to claim 39 which is not explicitly disclosed by Saint-Leger. As stated in In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977):

> Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Whether the rejection is based on 'inherency' under 35 U.S.C. § 102, on 'prima facie obviousness' under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products.

Example I of Saint-Leger reasonably appears to include the free form of a 1-hydroxy-2-pyridone, viz., OCTOPIROX, and an anionic surfactant. Applicants' specification states that when using the free form of the active ingredient, as Example 1 of Saint-Leger appears to be using, adjustment of pH to the skin-physiological range of approximately 4.5 to 6.5 is not necessary. (Specification, page 8, lines 29-33). Thus, it reasonably appears that Saint-Leger's Example 1 composition necessarily or inherently has a pH within the pH range of the composition recited in claim 38 and would not need to be adjusted to meet that range. Example 1 otherwise is identical to the claimed invention. On these facts, we believe that the evidence is sufficient to shift the burden of persuasion to applicants to show that the composition described in Example 1 of Saint-Leger does not necessarily or inherently have a pH within the range recited in claim 38. (Id.).

In any event, it would have been apparent to any person having ordinary skill in the art that the recited pH would be inherent in, or an obvious modification of, Saint-Leger's composition for use in treating a symptom of seborrheic dermatitis because Saint-Leger's composition is "formulated in a topically physiologically acceptable medium." (Saint-Leger, abstract). The Lange patent teaches using a physiologically acceptable acid in its second treatment phase. (Lange, abstract).[4] Lange states that the second phase "comprises a physiologically acceptable acid component, or mixture of such components." (Id.). Lange explains (column 5, lines 33-38):

> The acidity of the phase II solution is generally adjusted in the area of pH 3-6, preferred 4-5. The acidity of the phase II composition is adjusted in such a way that after application a situation is reached which is as much as possible in agreement with the natural pH of the skin.

Claim 40 limits claim 38 to at least one 1-hydroxy-2-pyridone or formula (I) comprising a cyclohexyl radical in the R^4 position. Saint-Leger teaches that a suitable antifungal agent for formulation according to his invention is CYCLOPIROX, i.e., 6-cyclohexyl-1-hydroxy-4-methyl-2-(1H)-pyridone (column 2, lines 28 and 29). Saint-Leger thus describes the 1-hydroxy-2-pyridone compound recited in claim 40.

Claim 48 depends from claim 38 and adds a limitation that "the pharmaceutical composition further comprises at least one additional surfactant chosen from anionic, cationic, nonionic, and amphoteric surfactants." In our judgment, that additional

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[4] As stated in In re Baxter Travenol Labs., 952 F.2d 388, 390, 21 USPQ2d 1281, 1284 (Fed. Cir. 1991), "extrinsic evidence may be considered when it is used to explain, but not expand, the meaning of a reference."

limitation does not serve to distinguish over Example 1 of Saint-Leger disclosing not only sodium lauryl ether sulfate containing 2.2 mol of ethylene oxide (anionic surfactant) but also coconut monoisopropanolamide (additional surfactant).

III. 35 U.S.C. § 103(a)

Claims 38-42, 48, and 53-66 are rejected under 35 U.S.C. § 103(a) in view of the combined teachings of Saint-Leger and Lange. The proper focus of an obviousness inquiry is whether "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." See Merck & Co., Inc. v. Biocraft Labs., Inc., 874 F.3d 804, 807, 10 USPQ2d 1843, 1846 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). The test for obviousness is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1971). Further, "in considering the disclosure of a reference, is it proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." In re Preda, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968).

Saint-Leger describes or reasonably would have suggested all aspects of the claimed invention for the reasons stated hereinabove except for the keratolytic agent of claims 53 and 59 and the lactic acid of claims 65 and 66. Saint-Leger discloses that

various types of adjuvants or additives are characteristically employed to formulate the compositions (column 3, lines 32-36). As stated by Saint-Leger (id., lines 38-43):

> Among these adjuvants or additives, especially representative are preservatives, stabilizing agents, pH regulators, osmotic pressure modifiers, emulsifying agents, sunscreen agents, antioxidants, fragrances, colorants, anionic, cationic, nonionic, amphoteric or zwitterionic surface-active agents or mixtures thereof, polymers, and the like.

Lange's invention "relates to the control of dandruff and similar scale forming conditions of the skin of the head" (column 1, lines 13-15). Lange discloses that "[o]ne may also use piroctone olamine [OCTOPIROX] in phase II because of its anti-seborrhoeic effect" (column 5, lines 65-66). Thus, Lange, like Saint-Leger, is directed to a method for treating a human patient with a symptom of seborrheic dermatitis.

Lange further discloses adding a keratolytic agent to his treatment composition. Lange teaches that organic acids, such as salicylic acid, "are known to give a therapeutic effect in the treatment of skin disease" (id., lines 24-32). Evidence submitted with the Reply Brief shows that salicylic acid was known as a keratolytic agent to persons having ordinary skill in the art at the time the invention was made. As indicated in the attached references, salicylic acid is a keratolytic agent. (Exhibit A, page 10; Exhibit B, page 166; Exhibit C, page 551). It would have been obvious for persons having ordinary skill in the art at the time the invention was made to add a keratolytic agent, like salicylic acid, to Saint-Leger's treatment compositions, to enhance their therapeutic effect.

Lange also discloses that lactic acid "plays an important physiological role in the structural stability and functional elasticity of the epidermis and keratine proteins" (column 8, lines 11-14). In that light, it would have been obvious for a person having ordinary skill in the art at the time the invention was made to add lactic acid to Saint-Leger's composition for its beneficial effects on the epidermis during treatment.

ORDER

For the reasons stated above, it is: ORDERED that

(1) the examiner's final rejections of claims 38-42, 48, and 53-66 are vacated; and

(2) new grounds of rejection are entered under the provisions of 37 CFR § 41.50(b).

This decision contains a new ground of rejection pursuant to 37 CFR § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 CFR § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 CFR § 41.50(b) also provides that the appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options

with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) *Reopen prosecution.* Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the proceeding will be remanded to the examiner. . . .
>
> (2) *Request rehearing.* Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

VACATED: 37 CFR § 41.50(b)

Sherman D. Winters
Administrative Patent Judge

Demetra J. Mills
Administrative Patent Judge

Lora Green
Administrative Patent Judge

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X. Related Proceedings Appendix

Appellants appealed to the Board once before during prosecution of the application on appeal and this appeal was assigned Appeal No. 2004-0309. The Board rendered its decision on Appeal No. 2004-0309 on September 15, 2004. Appellants also filed an Appeal Brief on October 15, 2007, in U.S. Application No. 10/606,229. The ongoing appeal in U.S. Application No. 10/606,229 has not yet been assigned an appeal number.